World Journal of Surgery and Surgical Research

Research Article
Published: 22 Jul, 2022

Pain Mitigation in Pediatric Endoscopies Using Virtual Reality and Intranasal Midazolam

Cecilia Mantegazza[1], Valentina Silvera[1], Luciano Maestri[2], Milena Meroni[2], Francesca Destro[2], Enrico La Pergola[2], Lucia Cococcioni[1], Elena Pozzi[1], Gloria Pelizzo[2,3] and Gianvincenzo Zuccotti[1,3]*

[1]Department of Pediatrics, V. Buzzi Children's Hospital, Italy

[2]Department of Pediatric Surgery, V. Buzzi Children's Hospital, Italy

[3]Department of Biomedical and Clinical Sciences, L. Sacco, University of Milan, Italy

Abstract

Introduction: Esophagogastroduodenoscopy (EGD) is a pain-related procedure with possible negative consequences in children. We aimed to prospectively compare three pain management approaches in deep sedated-EGD: Intravenous Midazolam (IVm), Virtual Reality (VR) +IVm, and Intranasal Midazolam (IN) +IVm, according to standard of care procedures.

Materials and Methods: 72 children aged between 4 and 18 years old were randomly assigned to one of the groups (30IV, 30VR, and 12IN). Age, sex and baseline Children Emotional Management Scale (CEMS) were collected. Primary outcomes of the study were the self-reported (Visual Analog Scale, VAS) and observed pain (Face, Legs, Activity, Cry, Consolability Scale, FLACC). Secondary outcomes were a combined VAS+FLACC scale, pain rated by parents (Numerical Rating Scale, NRS), operator's satisfaction, midazolam administered, presence of anterograde amnesia, time to discharge and side effects encountered. The Kruskal-Wallis and Fisher tests were used to test the effects of our interventions.

Results: No significant differences in age, sex and CEMS were encountered. The VR group reported significantly lower pain than IV and IN groups (median VAS VR:0, IV:2, IN:5, p=0.0045; median FLACC VR:2, IV:4, IN:3.5, p=0.0204; median VAS+FLACC VR:3, IV:7, IN:9.5, p=0.0002, median NRS VR:0, IV:2.5, IN:3.5, p=0.0003). Amnesia covered EGD + venipuncture in IN group (75%), but only EGD in VR and IV groups (100%) (p<0.001). Side effects occurred at a rate of 83% in IN, 56% in VR, 33% in IV (p=0.0115). No other significant differences were observed.

Conclusion: VR distraction reduces pain perception in children during EGD, without compromising the technical result of the procedure. This pilot study sets the stage for further investigations on the use of VR to improve pediatric patient's care and outcomes.

Keywords: Esophagogastroduodenoscopy; Pain; Virtual reality

OPEN ACCESS

Correspondence:
Cecilia Mantegazza, Department of Pediatrics, V. Buzzi Children's Hospital, Via Castelvetro 32, Milan, Italy, Tel: +0039263635329; E-mail: cecilia.mantegazza@asst-fbf-sacco.it

Received Date: *07 Jun 2022*
Accepted Date: *14 Jul 2022*
Published Date: *22 Jul 2022*

Citation:
Mantegazza C, Silvera V, Maestri L, Meroni M, Destro F, Pergola EL, et al. Pain Mitigation in Pediatric Endoscopies Using Virtual Reality and Intranasal Midazolam. World J Surg Surgical Res. 2022; 5: 1394.

Introduction

Esophagogastroduodenoscopy (EGD) is an essential, but invasive diagnostic procedure. It allows the detection of common gastrointestinal diseases such as celiac disease and its use in children is well established [1]. However, EGD can be a source of stress for children and their family and if not adequately aided by psychological and pharmacological support, it can result in emotional and psychological trauma. EGD-related stress triggers for the pediatric patient include hospitalization, waiting before the procedure, separation from parents and placement of venous access [2-4]. Inadequate pain prevention and anxiety may have long-term negative consequences, such as anticipatory anxiety during future procedures, lowering of the pain threshold, and future pain sensitization [2]. As an example, Pate et al. [5] study demonstrated that pain perceived by the children during medical procedures correlates significantly (p<0.0001) with fear and pain perceived as adults. When entered into a regression model, child pain accounted for more of the variance in adult fear than did child fear [5].

Different pharmacological and non-pharmacological methods, including immersive Virtual Reality (VR) and Intranasal (IN) midazolam, can potentially address these problems.

VR provides a tool for human/computer interaction, in which the human being becomes an

active participant in a virtual environment created through a Head-Mounted Display (HMD) [6]. The user is immersed and actively participates in the virtual environment as it changes in real time with his movements. The new generations of HMDs for VR have become a common technology, widely accessible, reasonably priced, and easy to use, also in a wide range of ages [2]. VR has already been shown to reduce stress and the perception of acute pain during different procedures, such as venipuncture [2,7], vaccinations or administration of anesthetics [8]. Its use has also been tested as a distraction method in children with painful wounds undergoing repeated dressing changes [9], among others. Only one study evaluated the use of VR in unsedated endoscopy but it is a retrospective study whose outcome was not the perceived pain but the feasibility of the endoscopy and the costs and time of the procedure [10].

IN midazolam is an effective preoperative sedative able to reduce anxiety and stress in children. In fact, midazolam is absorbed by many tissues, including the nasal mucosa, which offers an attractive non-invasive route of administration, as it does not involve the use of needles. IN midazolam in children reduces anxiety and mitigates uncooperative behavior, while offering a large safety margin [11]. Furthermore, in a dose range of 0.2 mg/kg to 0.6 mg/kg, IN midazolam induces sedation within 10 min to 20 min without serious side effects and it has been used for procedural sedation during laceration repairs [11,12], dental extractions [13,14], and as a premedication before total anesthesia [15], among others [16]. Just one study evaluated the efficacy of IN midazolam on fear and anxiety but no proper evaluation of pain through validated scales has been held [17]. Nevertheless, its use during EGD remains vastly unexplored.

Importantly, given their cost, acceptability and safety [10], both VR and IN midazolam, could be easily included in the standard practice in multiple pediatric hospitals as pain and anxiety addressing methods in different pediatric procedures, without requiring additional workload for health care providers [2].

The aim of our study was to assess the efficacy of VR or IN midazolam in reducing pain and EGD-related stress in children. To explore this, we have implemented our standard of care (IV midazolam), combining IV midazolam with VR or IN midazolam, and evaluated pain through validated scales, and assessed parent's and operator's satisfaction through the Likert scale.

Primary outcomes were the self-reported (Visual Analogue Scale, VAS) and observed pain (Face, Legs, Activity, Cry, Consolability Scale, FLACC). Secondary outcomes were a combined VAS+FLACC scale, pain rated by parents by a Numerical Rating Scale (NRS), increase in Heart Rate from basal level (HR), operator's and parent's satisfaction, total midazolam administered, presence of anterograde amnesia, time to discharge and side effects encountered.

To our knowledge, this is one of the first studies evaluating the effect of VR and IN midazolam on EGD-related pain and pave the way for further improvement in pediatric patients EGD.

Patients and Methods

Study design

This was a single center, three-arm parallel group, randomized controlled trial, conducted in accordance with the Declaration of Helsinki (as revised in Fortaleza, Brazil, October 2013).

Study setting and participants

This study was carried out in the pediatric endoscopy Unit of Buzzi Children's Hospital in Milan, Italy. Between November 2019 and December 2020, all children aged 4 to 18 years who underwent EGD and wished to participate to the study were enrolled after signing informed consent. Exclusion criteria were the following: Intellectual disability or neurocognitive disorder, a 3 or 4 American Society of Anesthesiologists (ASA) physical statuses [18].

Randomization, allocation concealment and blinding

Eligible participants were randomly assigned in a 1:1:1 ratio to one of three groups (group 1: IV midazolam, group 2: VR+IV midazolam, group 3: IN+IV midazolam). Randomization sequences were generated with a computerized random number generator by a research assistant. From March 2020 the administration of IN midazolam was no longer possible because of irritation of the nasal mucosa following nasopharyngeal swab for COVID-19. The staff performing EGD and the person who analyzed the data were blinded.

Devices

Virtual reality: Virtual reality was provided *via* a Head-Mounted Device (HMD, AODA-1068), a box with binocular glasses, where a Smartphone was inserted to run the appropriate applications. The HMD allowed 360° degrees animation in a three-dimensional and immersive way. The applications used were two: The "Safari Tours Adventures VR 4D" and the "Funny Farm VR"; children, regardless of age, could choose either type of virtual reality (Figure 1).

Mucosal atomization device: A Mucosal Atomization Device (MAD Nasal, Teleflex Medical) was used to administer midazolam intranasally (undiluted parenteral solution, 5 mg/ml); MAD is a device that creates a nebulization of the drug within the coannas and allows for faster absorption and greater bioavailability. The dose administered was as previously described [13] and comparable to the dose of midazolam administered IV (Figure 2) [19].

Study protocol

The study protocol is illustrated in Figure 3. Briefly, after randomization the following data was collected: sex, age, resting HR, and Children's Emotional Manifestation Scale (CEMS), to document children's emotional behavior during stressful medical procedure [20]. A non-blinded pediatric doctor and nurse were in charge of venous access placement, inserted in all children one hour after application of Eutectic Mixture of Local Anesthetics (EMLA) and sedation [21].

Group 1 received 0.3 mg/kg of midazolam IV (never exceeding a total dose of 10 mg) [22]; children belonging to group 2 were offered the use of VR during the venous access placement and during IV midazolam administration (0.3 mg/kg and never exceeding a total dose of 10 mg) [22]; group 3 received 15 min before needle insertion administration of IN midazolam (0.3 mg/kg, with a maximum dose of 5 mg) [23]. The level of sedation was then evaluated in all groups and EGD was performed only when an adequate level of sedation was achieved, defined as a Richmond Agitation-Sedation Scale (RASS) ≤-4 [24,25], whenever the RASS was > -4, then an extra dose of IV midazolam was administered (0.1 mg/kg per dose, repeatable up to maximum total dose of 0.5 mg/kg and never exceeding a total dose of 10 mg) [22]. EGD was then performed by a blinded team composed of a pediatric trained endoscopist or a pediatric surgeon, assisted by at least two nurses.

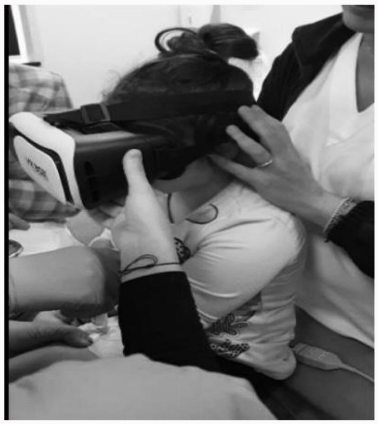

Figure 1: Child experiencing VR during venous access placement.

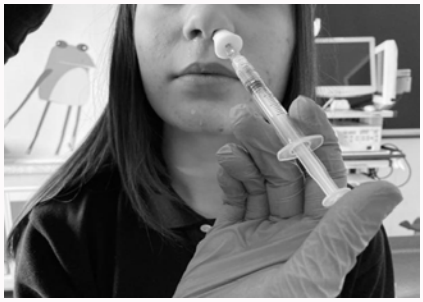

Figure 2: Child during midazolam IN administration.

Pain assessment

During the procedure the FLACC scale was used by trained nurses to measure the child's perceived pain [26]. The FLACC scale (Figure 4) is a behavioral scale for measuring pain that has been validated in children who are too young (under three years of age) or unable to verbalize or self-report their pain [27]. It's also used as a procedural pain assessment tool in children aged 5 to 16 years [28].

The maximum HR value was also recorded. After EGD the following information were collected: the child was asked to score the pain perceived through the VAS scale (Figure 5), that has been shown to be a reliable self-assessment method for pain intensity and anxiety in children between 2 and 17 years of age [29,30], while the parents were asked to rate their child's perceived pain using the NRS scale (Figure 6), which is used in children aged ≥ 8 years and for parental assessment of pain in the child [30].

The VAS scale is a 10 cm horizontal line marked with two dots: the one at the beginning corresponds to "no pain" and the one at the end corresponds to the "worst possible pain". The child is asked to make a line describing his or her level of pain [31].

The NRS is a 11 point (0-10) scale where the end points are the extremes of no pain and pain as bad as it could be, or worst pain [31].

Other outcomes

The total amount of midazolam administered to reach deep sedation was recorded. To determine the children's degree of amnesia the last thing remembered before the EGD was registered. Amnesia was considered complete when it included the venipuncture and EGD, partial including EGD or venipuncture, or none. The operator's and parent's satisfaction were measured through a 4-point Likert scale (4= "very satisfied," 3= "satisfied," 2= "dissatisfied," 1=" very dissatisfied") and the GHAA-9m questionnaire (the validated Italian version of the GHAA-9m questionnaire developed by the American Society of Gastrointestinal Endoscopy) respectively [30,32]. The GHAA-9 m questionnaire's answerers (Figure 7) were analyzed as follows: 1= "Poor", 2= "Fair", 3= "Good", 4= "Very Good", 5= "Excellent".

All adverse events (hiccups, double vision, paradoxical reaction, nausea or vomiting, lesions in the oral cavity or other locations, burning sensation) encountered during or in the 48 h after the procedure, and the time between the end of the procedure and the ability to drink water (time of discharge) were also collected.

Data analysis

Descriptive statistic was applied wherever required. Continuous variables were reported as median [interquartile range]. Categorical data were presented as absolute frequencies and percentages.

The nonparametric Kruskal-Wallis test and the Fisher's exact test were used to assess the effect of different treatments. Multiple comparisons were performed with Wilcoxon test without a formal control of the overall Type I error probability. P values were used as measure of statistical evidence with a non-formal threshold al 0.05 and Bonferroni correction was considered for correcting for test multiplicity. The software SAS JMP Pro 16.0.0 was used to carry out the statistical analysis.

Results

Between November 2019 and December 2020, 117 EGD were performed, 45 did not meet inclusion criteria. Seventy-two children were then enrolled in the study and included in the data analysis (IV group: n.30, VR group: n.30, IN group n.12). No relevant differences were found between the three groups in age, sex and CEMS (Table 1).

Primary outcomes

We observed a significant difference between the distribution of VAS and FLACC in the three groups (Table 2). In particular we encountered a lower VAS in the IV and VR group, compared to IN administration of midazolam, and a significantly lower FLACC in the VR group compared to the IV (Table 2), following Wilcoxon unpaired two-sample test statistic for multiple comparisons.

Secondary outcomes

We found a difference between the distribution of the subjective-objective combined pain scale, the NRS and parent's satisfaction Likert scale (Table 2). In particular we observed that VAS+FLACC level and NRS were significantly lower, while parent's satisfaction was significantly higher in the VR group, compared to the IN and the IV groups (Table 3), following Wilcoxon unpaired two-sample test statistic for multiple comparisons.

Adverse events were encountered in 83.5%, 33.3% and 56.7% of children in the IN, IV and VR group respectively (p=0.0115).

Complete amnesia was experienced in 75% of children belonging to the IN group, while no amnesia affected the others; partial amnesia

Table 1: Demographics and CEMS.

	Age	Sex	CEMS	N
Group 1 (IV)	13.5 years (7.2-14.6)	M 53.3% F 46.7%	5.5 (5-6.3)	30
Group 2 (VR+IV)	12 years (7.7-13.7)	M 60% F 40%	6 (5-7)	30
Group 3 (IN+IV)	10.1 years (8-13.8)	M 66.7% F 33.3%	5.5 (5-6.8)	12

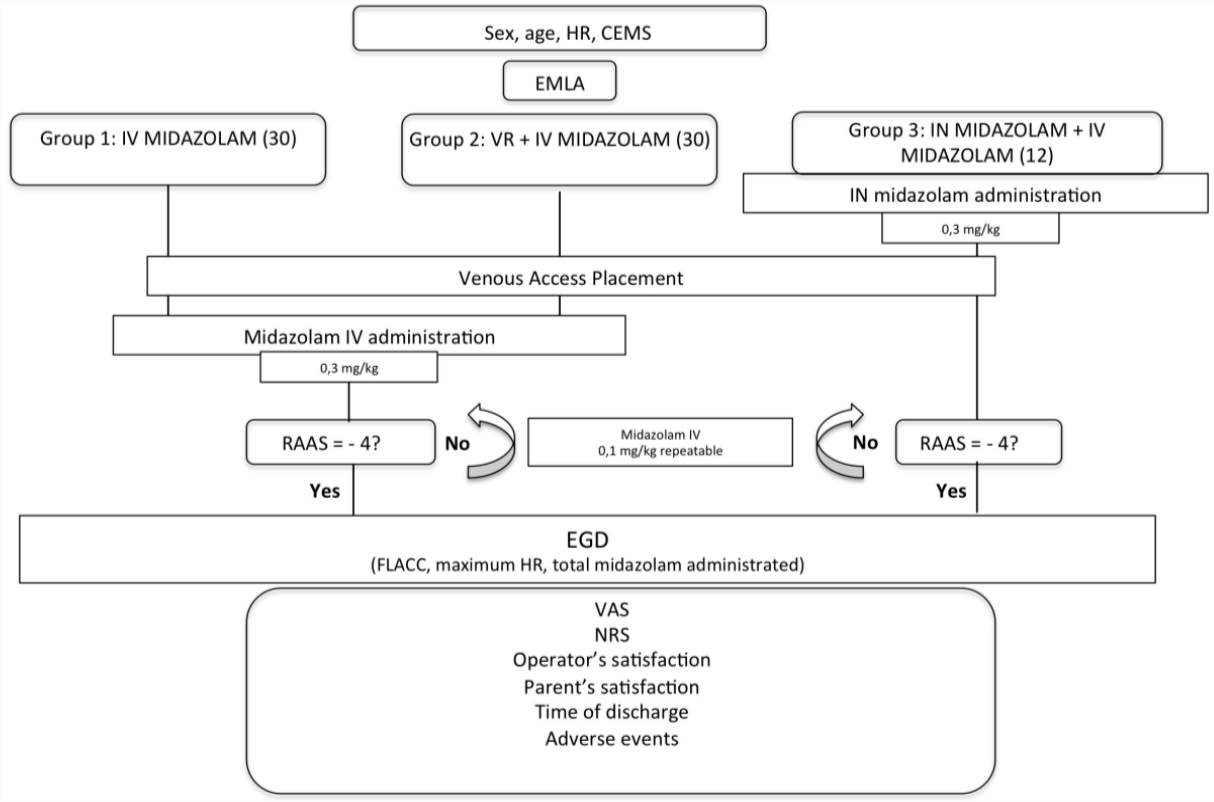

Figure 3: The study flowchart.
CEMS: Children's Emotional Manifestation Scale; RASS: Richmond Agitation-Sedation Scale; FLACC: Face, Legs, Activity, Cry, Consolability Scale; VAS: Visual Analogue Scale; NRS: Numerical Rating Scale

Category	Scoring		
	0	1	2
Face	No particular expression or smile	Occasional grimace or frown, withdrawn, disinterested	Frequent to constant quivering chin, clenched jaw
Legs	Normal position or relaxed	Uneasy, restless, tense	Kicking or legs drawn up
Activity	Lying quietly, normal position moves easily	Squirming, shifting back and forth, tense	Arched, rigid, or jerking
Cry	No cry (awake or asleep)	Moans or whimpers; occasional complaint	Crying steadily, screams or sobs, frequent complaints
Consolability	Content, relaxed	Reassured by occasional touching, hugging or being talked to, distractible	Difficult to console or comfort

Figure 4: FLACC scale.

Table 2: Median, quartile, chi-squared test and Kruskal-Wallis test of the following parameters: VAS, FLACC, VAS+FLACC, NRS, operator's and parent's Likert scales, maximum/resting HR, total midazolam administered, time to discharge, of all three interventions; *p <0.05.

	Group n	Median 1st and 3rd Q	Sum of Ranks Mean Rank	p chi squared
VAS	IN	5	626	0.0045*
	12	2.25-7	52.2	
	IV	2	1107.5	
	30	0-5	36.9	
	VR	0	895.5	
	30	0-3	29.8	
FLACC	IN	3.5	495	0.0204*
	12	1.25-9	41.2	
	IV	4	1280	
	30	3-7	42.7	
	VR	2	853	
	30	0-5.25	28.4	
VAS+FLACC	IN	9.5	616.5	0.0002*
	12	5.75-12	51.37	
	IV	7	1257 4	
	30	4-10	1.9	
	VR	3	754.5	
	30	1-6	25.15	
NRS	IN	3.5	594.5	0.0003*
	12	1.25-6.75	49.5	
	IV	2.5	1258.5	
	30	0-5.625	41.5	
	VR	0	775	
	30	0-1	25.8	
Parent's Satisfaction	IN	31	364.5	0.0175*
	12	29.25-32	30.4	
	IV	30	921.5	
	30	27.75-33	30.7	
	VR	33	1342	
	30	31.75-33.25	44.7	
Operator's Satisfaction	IN	3	308	0.0648
	12	3-4	25.7	
	IV	4	1129.5	
	30	3-4	37.6	
	VR	4	1190.5	
	30	3-4	39.7	
Maximum/resting HR	IN	1.56	519.5	0.1224
	12	1.38-1.77	43.3	
	IV	1.54	1187	
	30	1.33-1.74	39.6	
	VR	1.42	921.5	
	30	1.24-1.74	30.7	
Total Midazolam(mg)	IN	10	435.5	0.9066
	12	8.125-10	37.8	
	IV	10	1062.5	
	30	7-10	35.4	
	VR	10	1112	
	30	8.5-10	37.1	
Time to Discharge (min)	IN	95	413	0.8678
	12	72.5-135	34.4	
	IV	105	1137.5	
	30	90-132.5	37.9	
	VR	100	1077.5	
	30	90-130	35.9	

covered all children in the IV and VR (p<0.001).

Discussion

EGD is routinely performed in ambulatory settings as a diagnostic tool for assessing gastrointestinal diseases in children. The mechanism of pain/anxiety related to invasive procedure is complex, and there are many influencing factors [33]. Researchers have considered different pharmacological and non-pharmacological methods to reduce pain, such as acetaminophen, benzodiazepines, and opioids, and novel technologies, among which VR [34]. Compared to traditional treatment, multimodal analgesia is an interdisciplinary approach to pain management that can maximize the positive effects of the treatment, while decreasing the associated adverse effects [35].

The ideal analgesic for outpatient procedures should provide adequate pain control with absence of significant adverse effects.

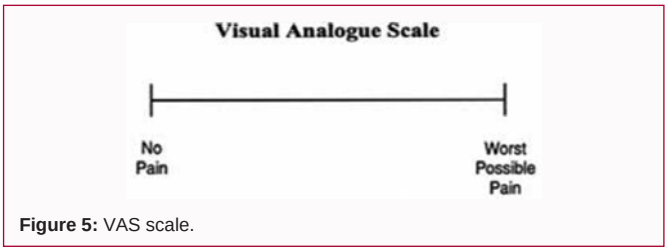

Figure 5: VAS scale.

Figure 6: NRS scale.

Results obtained in this study support the use of VR distraction as an adjuvant to pharmacologic analgesia, showing that VR is effective in minimizing pain perception and stress intensity during EGD in children. Our data demonstrates that playing the VR had a positive effect on pain and anxiety evaluated by an objective scale, a mixed subjective and objective scale and pain rated by parents, while a positive effect of VR on parent's satisfaction was also uncovered. Nevertheless, we did not observe any difference between VR and IV group based on the VAS scale; however VAS may be unreliable due to the post-amnesia effect of midazolam.

Importantly, operator's satisfaction, total midazolam administered and time to discharge were not affected by the use of VR glasses, so no obstacles to investigating VR further in a larger sample of patients have been highlighted.

Our study also shows that although IN combined with IV midazolam ensured a complete retrograde amnesia in children, it was less effective in pain mitigation and associated with a higher rate of adverse events compared to IV midazolam either alone or combined with VR.

The results of this study are not surprising; indeed, VR distraction is an emerging non-pharmacologic and non-invasive analgesic that modulates pain perception, by diverting the patient attention [36]. Thanks to the HMD devices, VR is a tool through which the patient can have an active and more engaging participation, it prevents the view of the surrounding environment, which can be a source of anxiety, with minimal engagement of body movement; therefore user has less attention available to process signals from pain receptors, while no interference with the procedure has been encountered [37]. In children, different studies demonstrated that immersion in VR during blood sampling [8] and dental/periodontal procedures [38], significantly mitigated pain intensity. The same advantage was however not confirmed in two trials of VR in burn wound victims, where the authors suggested the development of a better-customized instrument to solve the issue [39,40]. However this could be due to the different degree of pain perceived in the different procedures: it could therefore be hypothesized that VR can be used in procedures with low to moderate perceived pain. Very little is known regarding the effect of VR in endoscopy, especially in children. In adults, visual and/or auditory distraction during endoscopic procedures reduces

Table 3: Wilcoxon unpaired two-sample test.

	VAS		FLACC		VAS+FLACC		NRS		Parent satisfaction	
	Median Score Difference (DS)	p	Median Score Difference (DS)	p	Median Score Difference (DS)	p	Median Score Difference (DS)	p	Median Score Difference (DS)	p
VR-IV	-5.9 (4.2)	0.1584	-11.9 (4.5)	0.0077*	-14.7 (4.5)	0.0011*	-13.4 (4.1)	0.0012*	10.4 (4.4)	0.0193*
IV-IN	-8.9 (4.1)	0.0286*	0.6 (4.2)	0.8884	-6.8 (4.2)	0.1021	-4.3 (4.1)	0.2876	-1.8(4.1)	0.6639
VR-IN	-12.9 (4.0)	0.0012*	-7.2 (4.1)	0.0809	-13.9 (4.2)	0.0009*	-13.7 (3.8)	0.0003*	10.3(4.1)	0.0117*

*p<0.05 (0.0033 after Bonferroni's correction)

Questionnaire

A number of questions are listed below regarding the visit you just made. In terms of your satisfaction, how would you rate each of the following:

1. How long you waited to get an appointment
□ Excellent □ Very Good □ Good □ Fair □ Poor

2. Lenght of time spent waiting at the office/hospital for the procedure
□ Excellent □ Very Good □ Good □ Fair □ Poor

3. The personal manner (courtesy, respect, sensitivity, friendliness) of the physician who performed your procedure
□ Excellent □ Very Good □ Good □ Fair □ Poor

4. The technical skills (thoroughness, carefulness, competence) of the physician who performed your procedure
□ Excellent □ Very Good □ Good □ Fair □ Poor

5. The personal manner (courtesy, respect, sensitivity, friendliness) of the nurses and other supportive staff
□ Excellent □ Very Good □ Good □ Fair □ Poor

6. Adequacy of explanation of what was done for you and all your questions answered
□ Excellent □ Very Good □ Good □ Fair □ Poor

7. Overall rating of the visit
□ Excellent □ Very Good □ Good □ Fair □ Poor

8. Would you have the procedure done again by this physician?
□ Excellent □ Very Good □ Good □ Fair □ Poor

9. Would you consider having this procedure again at this facility?
□ Excellent □ Very Good □ Good □ Fair □ Poor

Figure 7: GHAA-9 m questionnaire.

pain and improves satisfaction [41]. In children a retrospective study of almost 200 patients found that VR allowed un-sedated trans-nasal gastroscopy, moreover the procedure was safe and cost-effective for staging of eosinophilic oesophagitis [10]. However no pain evaluation was performed.

Although sedation avoidance may be beneficial to prevent complications, in particular cardiopulmonary ones, current ESGE/ESPGHAN guidelines recommend EGD to be performed under general anesthesia or, if not feasible under deep sedation in children. Therefore, at the moment EGD pain management cannot be solely based on VR [1]. Nevertheless, VR distraction could be used as an adjuvant to pharmacologic analgesia to lower the dose of analgesics required and reducing the risk of sedation-related complications. Although our study did not observe a correlation between total midazolam administered and VR, the efficacy of visual distraction in reducing the required medication dose has already been shown in adults undergoing colonoscopy and represents an attractive avenue for further studies to improve pediatric endoscopy [41].

This study observed that although IN midazolam provided complete amnesia it had no effect on perceived pain. These data is in line with a study published by Fishbein et al. [17], where IN midazolam proved to be a sedative capable of reducing anxiety due to separation from parents but did not diminish negative behaviors during EGD. This lack of efficacy could be linked to a possible run-off of the drug from the nasal cavity, due to mucosal surface saturation, leading to swallowing of the administered medication, gastrointestinal absorption, first-pass metabolism, and decreased bioavailability [42]. To avoid run-off, concentrated medication administered in therapeutic doses of maximum 1 mL per nostril should be used, moreover doses should always be separated in those children weighing more than 20 kg for 5 mg/mL midazolam [43]. In addition, lack of efficacy of IN midazolam could be due to the dose administered, which per institutional policy, in our study has never exceeded 0.3 mg/kg, but could be increased to 0.5 mg/kg. Nevertheless, it is important to mention that the IN group experienced more frequent adverse events, which leads us to hypothesize that an increase in dosage could exacerbate this effect. However, the absence of significant systemic adverse reactions in the literature when solely IN midazolam is administered has to be outpointed [43,44].

We acknowledge that out study have some limitations. These includes involving a small sample of patients which precluded us from inferring robust statements on clinically relevant endpoints; additionally, subjective pain score was collected following recovery

from sedation, relying on recalled pain, which could have been affected by the midazolam-induced amnesia, however this was combined by more reliable FLACC evaluation by trained nurses. Finally, age may have influenced the reaction to the different treatments and due to the small sample enrolled, we were not able to split children into subgroups.

Conclusion

The data collected in this study suggest that VR distraction during sedated EGD is effective in children in reducing pain perception, without compromising the technical success of the procedure. This study also suggests that VR should be adopted as a clinical intervention in combination with IV sedation for pain and stress management on a regular basis due to the low costs and widely availability of the device. This study has not identified any obstacles to investigating VR glasses further in a large multicenter study, which would allow evaluating age-related differences in treatment efficacy.

In conclusion, our work has set the stage for the evaluation of VR in EGD in pediatric patients, an intervention with the potential to contribute to tangible improvements in patient care.

Acknowledgement

The authors would like to acknowledge all the nursing trained staff (Serafina Albano, Elena Valleriani, Fulvia Rossi, Nunzia Rea, Teresa Principalli, Cinzia Barlera, Paola Poletto, Martina Alvarez) and Leonardo Filoni who contributed to the realisation of this study.

References

1. Tringali A, Thomson M, Dumonceau JM, Tavares M, Tabbers MM, Furlano R, et al. Pediatric gastrointestinal endoscopy: European Society of Gastrointestinal Endoscopy (ESGE) and European Society for Paediatric Gastroenteology Hepatology and Nutrition (ESPGHAN) Guideline Executive summary. Endoscopy. 2017;49(1):83-91.
2. Wong CL, Lui MMW, Choi KC. Effects of immersive virtual reality intervention on pain and anxiety among pediatric patients undergoing venipuncture: A study protocol for a randomized controlled trial. Trials. 2019;20(1):1-10.
3. Cunliffe M, Roberts SA. Pain management in children. Curr Anaesth Crit Care. 2004;15(4-5):272-83.
4. American Academy of Pediatrics. Committee on Psychosocial Aspects of Child and Family Health; Task Force on Pain in Infants, Children, and Adolescents. The assessment and management of acute pain in infants, children, and adolescents. Pediatrics. 2001;108(3):793-7.
5. Pate JT, Blount RL, Cohen LL, Smith AJ. Childhood medical experience and temperament as predictors of adult functioning in medical situations. Children's Health Care. 1996;25(4):281-98.
6. Won A, Bailey J, Bailenson J, Tataru C, Yoon I, Golianu B. Immersive virtual reality for pediatric pain. Children. 2017;4(7):52.
7. Piskorz J, Czub M. Effectiveness of a virtual reality intervention to minimize pediatric stress and pain intensity during venipuncture. J Spec Pediatr Nurs. 2018;23(1).
8. Chan E, Hovenden M, Ramage E, Ling N, Pham JH, Rahim A, et al. Virtual reality for pediatric needle procedural pain: Two randomized clinical trials. J Pediatr. 2019;209:160-7.
9. Schmitt YS, Hoffman HG, Blough DK, Patterson DR, Jensen MP, Soltani M, et al. A randomized, controlled trial of immersive virtual reality analgesia, during physical therapy for pediatric burns. Burns. 2011;37(1):61-8.
10. Nguyen N, Lavery WJ, Capocelli KE, Smith C, DeBoer EM, Deterding R, et al. Transnasal endoscopy in unsedated children with eosinophilic esophagitis using virtual reality video goggles. Clin Gastroenterol Hepatol. 2019;17(12):2455-62.
11. Yealy DM, Ellis JH, Hobbs GD, Moscati RM. Intranasal midazolam as a sedative for children during laceration repair. Am J Emerg Med. 1992;10(6):584-7.
12. Connors K, Terndrup TE. Nasal versus oral midazolam for sedation of anxious children undergoing laceration repair. Ann Emerg Med. 1994;24(6):1074-9.
13. Gentz R, Casamassimo P, Amini H, Claman D, Smiley M. Safety and efficacy of 3 pediatric midazolam moderate sedation regimens. Anesth Prog. 2017;64(2):66-72.
14. Al-Rakaf H, Bello LL, Turkustani A, Adenubi JO. Intranasal midazolam in conscious sedation of young paediatric dental patients. Int J Paediatr Dent. 2001;11(1):33-40.
15. Karl HW, Keifer AT, Rosenberger JL, Larach MG, Ruffle JM. Comparison of the safety and efficacy of intranasal midazolam or sufentanil for preinduction of anesthesia in pediatric patients. Anesthesiology. 1992;76(2):209-15.
16. Harcke HT, Grissom LE, Meister MA. Sedation in pediatric imaging using intranasal midazolam. Pediatr Radiol. 1995;25(5):341-3.
17. Fishebein M, Lugo R, Woodland J, Lininger B, Linscheid T. Evaluation of intranasal midazolam in children undergoing esophagogastroduodenoscopy. J Pediatr Gastroenterol Nutr. 1997;25(3):261-6.
18. Gilger MA. Conscious sedation for endoscopy in the pediatric patient. Gastroenterol Nurs. 1993;16(2):75-9.
19. Hogberg L, Nordvall M, Tjellstrom B, Stenhamma L. Intranasal versus intravenous administration of midazolam to children undergoing small bowel biopsy. Acta Paediatr. 1995;84(12):1429-31.
20. Li, HCW, Lopez V. Children's emotional manifestation scale: Development and testing. J Clin Nurs. 2005;14(2):223-9.
21. Blount RL, Piira T, Cohen LL, Cheng PS. Pediatric procedural pain. Behav Modif. 2006;30(1):24-49.
22. Krauss B, Green SM. Procedural sedation and analgesia in children. Lancet. 2006;367(9512):766-80.
23. Fantacci C, Fabrizio GC, Ferrara P, Franceschi F, Chiaretti A. Intranasal drug administration for procedural sedation in children admitted to pediatric emergency room. Eur Rev Med Pharmacol Sci. 2018;22(1):217-22.
24. Kerson AG, DeMaria R, Mauer E, Joyce C, Gerber LM, Greenwald BM, et al. Validity of the Richmond Agitation-Sedation Scale (RASS) in critically ill children. J Intensive Care. 2016;4:65.
25. Rosenberg L, Traube C. Sedation strategies in children with Pediatric Acute Respiratory Distress Syndrome (PARDS). Ann Transl Med. 2019;7(19):509.
26. Crellin DJ, Harrison D, Santamaria N, Huque H, Babl FE. The psychometric properties of the FLACC scale used to assess procedural pain. J Pain. 2018;19(8):862-72.
27. Johansson M, Kokinsky E. The COMFORT behavioral scale and the modified FLACC scale in pediatric intensive care. Nurs Crit Care. 2009;14(3):122-30.
28. Nilsson S, Finnstro B, Kokinsky E. The FLACC behavioral scale for procedural pain assessment in children aged 5-16 years. Paediatr Anaesth. 2008;18(8):767-74.
29. Ozkan TK, Polat F. The effect of virtual reality and kaleidoscope on pain and anxiety levels during venipuncture in children. J Perianesth Nurs. 2020;35(2):206-11.
30. Annequin D, Carbajal R, Chauvin P, Gall O, Tourniaire B, Murat I. Fixed

50% nitrous oxide oxygen mixture for painful procedures: A French survey. Pediatrics. 2000;105(4):E47.

31. Williamson A, Hoggart B. Pain: A review of three commonly used pain rating scales. J Clin Nurs. 2005;14(7):798-804.

32. Petitti T, Candela ML, Ianni A, De Belvis AG, Ricciardi W, De Marinis MG. Validation of the Italian version of the GHAA-9 m questionnaire on patient satisfaction in digestive Endoscopy. Ig Sanita Pubbl. 2015;71(5):465-76.

33. Franck LS, Greenberg CS, Stevens B. Pain assessment in infants and children. Pediatr Clin North Am. 2000;47(3):487-512.

34. Young KD. Pediatric procedural pain. Ann Emerg Med. 2005;45(2):160-71.

35. Horlocker TT, Kopp SL, Pagnano MW, Helb JR. Analgesia for total hip and knee arthroplasty: A multimodal pathway featuring peripheral nerve block. J Am Acad Orthop Surg. 2006;14(3):126-35.

36. Eccleston C, Crombez, G. Pain demands attention: A cognitive-affective model of the interruptive function of pain. Psychol Bull. 1999;125(3):356-66.

37. Hoffman HG, Chambers GT, Meyer WJ, Arceneaux LL, Russell WJ, Seibel EJ, et al. Virtual reality as an adjunctive non-pharmacologic analgesic for acute burn pain during medical procedures. Ann Behav Med. 2011;41(2):183-91.

38. Atzori B, Lauro GR, Giugni A, Calabro M, Alhalabi W, Hoffman HG, et al. Virtual reality analgesia for pediatric dental patients. Front Psychol. 2018;9:2265.

39. Kipping B, Rodger S, Miller K, Kimble RM. Virtual reality for acute pain reduction in adolescents undergoing burn wound care: A prospective randomized controlled trial. Burns. 2012;38(5):650-7.

40. Morris LD, Louw QA, Crous LC. Feasibility and potential effect of a low-cost virtual reality system on reducing pain and anxiety in adult burn injury patients during physiotherapy in a developing country. Burns. 2010;36(5):659-64.

41. Lee DWH, Chan ACW, Wong SKH, Fung TMK, Li ACN, Chan SKC, et al. Can visual distraction decrease the dose of patient-controlled sedation required during colonoscopy? A prospective randomized controlled trial. Endoscopy. 2004;36(3):197-201.

42. Dale O, Hjortkjaer R, Kharasch ED. Nasal administration of opioids for pain management in adults. Acta Anaesthesiol Scand. 2002;46(7):759-70.

43. Wolfe TR, Braude DA. Intranasal medication delivery for children: A brief review and update. Pediatrics. 2010;126(3):532-7.

44. McGrath PA, Seifert CE, Speechley KN, Booth JC, Stitt L, Gibson MC. A new analogue scale for assessing children's pain: An initial validation study. Pain. 1996;64(3):435-443.