Review on sedation for gastrointestinal tract endoscopy in children by non-anesthesiologists

Rok Orel, Jernej Brecelj, Jorge Amil Dias, Claudio Romano, Fernanda Barros, Mike Thomson, Yvan Vandenplas

Rok Orel, Jernej Brecelj, Children’s Hospital, University Medical Centre Ljubljana, and Medical Faculty, University of Ljubljana, 1000 Ljubljana, Slovenia

Jorge Amil Dias, Department of Pediatrics, Hospital S. João, 4202-451 Porto, Portugal

Claudio Romano, Pediatric Department, University of Messina, 98122 Messina, Italy

Fernanda Barros, Chair of the Paediatric Section of the Portuguese Society of Anaesthesiology, Department of Anaesthesiology, Hospital S. João, 4202-451 Porto, Portugal

Mike Thomson, Centre for Paediatric Gastroenterology, International Academy of Paediatric Endoscopy Training, Sheffield Children’s Hospital, Weston Bank, Sheffield S10 2TH, United Kingdom

Yvan Vandenplas, Department of Pediatrics, UZ Brussel, Vrije Universiteit Brussel, 1090 Brussels, Belgium

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Correspondence to: Yvan Vandenplas, MD, PhD, Department of Pediatrics, UZ Brussel, Vrije Universiteit Brussel, Laarbeeklaan 101, 1090 Brussels, Belgium. yvan.vandenplas@uzbrussel.be
Telephone: +32-24-775780
Fax: +32-24-775783

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Abstract

AIM: To present evidence and formulate recommendations for sedation in pediatric gastrointestinal (GI) endoscopy by non-anesthesiologists.

METHODS: The databases MEDLINE, Cochrane and EMBASE were searched for the following keywords “endoscopy, GI”, “endoscopy, digestive system” AND “sedation”, “conscious sedation”, “moderate sedation”, “deep sedation” and “hypnotics and sedatives” for publications in English restricted to the pediatric age. We searched additional information published between
January 2011 and January 2014. Searches for (upper) GI endoscopy sedation in pediatrics and sedation guidelines by non-anesthesiologists for the adult population were performed.

RESULTS: From the available studies three sedation protocols are highlighted. Propofol, which seems to offer the best balance between efficacy and safety is rarely used by non-anesthesiologists mainly because of legal restrictions. Ketamine and a combination of a benzodiazepine and an opioid are more frequently used. Data regarding other sedatives, anesthetics and adjuvant medications used for pediatric GI endoscopy are also presented.

CONCLUSION: General anesthesia by a multidisciplinary team led by an anesthesiologist is preferred. The creation of sedation teams led by non-anesthesiologists and a careful selection of anesthetic drugs may offer an alternative, but should be in line with national legislation and institutional regulations.

Key words: Gastro-intestinal endoscopy; Gastroscopy; Colonoscopy; Sedatives; Pediatric ages; Anesthetics; Analgesics

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Core tip: Sedation for pediatric gastro-intestinal endoscopy is preferably performed by pediatric anesthesiologists, as part of a multidisciplinary team. However, in many hospitals pediatric anesthesiology is insufficiently developed. The creation of sedation teams led by non-anesthesiologists and a careful selection of anesthetic drugs may offer an effective and safe alternative. These teams should be in line with national legislation and institutional regulations. This paper will help non-anesthesiologists to provide as good-as-possible sedation for children undergoing endoscopy. Practical protocols were developed providing up-to-date information on the most effective and most safe options.

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INTRODUCTION
Esophago-gastro-duodenoscopy in children needs almost always to be performed under anesthesia or deep sedation. Procedural analgesia and sedation for procedures performed in ambulatory care are changing. The authors reviewed the literature on sedation and for endoscopy by non-anesthesiologists and to propose practical algorithms.

In order to obtain the greatest yield from a pediatric gastrointestinal (GI) endoscopic procedure and to perform these with the highest quality and with the maximum level of safety, some prerequisites must be fulfilled. A pediatric gastroenterologist or dedicated pediatrician must have judged the necessity of the procedure to optimize patient management. The procedure must be performed by a skilled endoscopic team with appropriate equipment in a suitable environment. The patient and parents or guardians must be informed as much and good as possible.

General anesthesia is only possible in a limited number of centers because of shortness of anesthesiologists. The aim of this review is to present and discuss different sedation protocols for non-anesthesiologists for pediatric GI endoscopies. Several protocols for procedural sedation by non-anesthesiologists have been produced by different professional bodies and organizations. However, practical algorithms for these procedures have not been published.

MATERIALS AND METHODS
The search for studies on pediatric sedation for GI endoscopy was an update of van Beek and Leroy’s search strategy for the period between January 2011 (when their search was finished) and January 2014 and utilized the following databases: MEDLINE, Cochrane, and EMBASE. These were searched for the keywords "endoscopy, GI", "endoscopy, digestive system" and "sedation", "conscious sedation", "moderate sedation", "deep sedation" and "hypnotics and sedatives" for publications in English restricted to the pediatric age group, which was defined as 0 to 18 years. Subsequently a search for pediatric GI endoscopy sedation guidelines for the same keywords as above for the last 20 years with the same limits (publications in English, pediatric population) was undertaken. The search was expanded to include guidelines for GI endoscopy sedation by non-anesthesiologists for the adult population for the last 10 years. Furthermore a search for guidelines for pediatric procedural sedation published in the last 10 years was made.

RESULTS
The first search revealed 12 studies of which 8 are listed in Table 1. Four of them were not relevant: Liu et al analyzed anesthesia for outpatient gastroscopies and colonoscopies in adults only, Yen et al studied sex differences in sedation with midazolam and alfentanil for gastroscopy only in adults, too. The aim of the study of Vadlamudi et al was evaluation of ileoscopy via stoma and not a sedation. And finally, Siwiec et al tested transnasal gastroscopy with ultrathin endoscope in non-sedated healthy volunteers or patients with the signs or symptoms of gastro-esophageal reflux disease.

We found one guideline for pediatric GI endoscopy in
Table 1 Publications from the first search (“endoscopy, gastrointestinal”, “endoscopy, digestive system” AND “sedation”, “conscious sedation”, “moderate sedation”, “deep sedation”, and “hypnotics and sedatives”; limits: publications in English, paediatric population)

| Ref.          | Methodology                          | Results                                                                 | Limitations                                      | Conclusions                              |
|--------------|--------------------------------------|------------------------------------------------------------------------|--------------------------------------------------|------------------------------------------|
| Bedirli et   | Study type: prospective, randomised,| Adverse events: self-limited bradycardia and transient                  | Only one dosage of drugs instead of               | Propofol with tramadol or propofol       |
| al[3]        | double-blinded                        | desaturation in age group 0-2 yr, more in the fentanyl group           | titrating them                                    | provided efficient sedation; significantly|
|              | Patients: N = 80; 1–16 yr; ASA 1, II |                          Effectiveness: lower sedation scores in tramadol group; no  | less adverse effects in the tramadol           | less adverse effects in the tramadol      |
|              | Procedure: upper GI endoscopy        | difference of gastroenterologist rating                                | group                                            | group                                    |
|              | Drugs: baseline: propofol (1 mg/kg; |                          |                                                  |                                          |
|              | additional 0.5–1 mg/kg as needed;   |                                                  |                                                  |                                          |
|              | intervention: fentanyl (2 μg/kg) vs  |                                                  |                                                  |                                          |
|              | tramadol (2 mg/kg)                  |                                                  |                                                  |                                          |
|              | Intended sedation level: deep sedation |                                                  |                                                  |                                          |
|              | Additional interventions: spray of   |                                                  |                                                  |                                          |
|              | lidocaine 10%; infusion of 10 L    |                                                  |                                                  |                                          |
|              | Ringer’s solution (10 mL/kg per     |                                                  |                                                  |                                          |
|              | hour); supplemental oxygen 3–4 L/   |                                                  |                                                  |                                          |
|              | min)                                 |                                                  |                                                  |                                          |
|              | Administered by: anesthesiologist   |                                                  |                                                  |                                          |
|              | Outcome measures:                   |                                                  |                                                  |                                          |
|              | Adverse events: HR (change for 20%   |                                                  |                                                  |                                          |
|              | from the baseline), BP (change for  |                                                  |                                                  |                                          |
|              | 20% from the baseline), SpO2 (< 90%  |                                                  |                                                  |                                          |
|              | for more than 15 s), respiratory rate, agitation score |                                                  |                                                  |                                          |
|              | Effectiveness: Ramsey sedation score, |                                                  |                                                  |                                          |
|              | duration of endoscopy, Steward        |                                                  |                                                  |                                          |
|              | recovery score, endoscopist’s rating|                                                  |                                                  |                                          |
|              | of ease of procedure, total propofol|                                                  |                                                  |                                          |
|              | consumption                           |                                                  |                                                  |                                          |
|              |                                      |                                                  |                                                  |                                          |
| Breccelj et  | Study type: randomized, controlled,  | Adverse events: mild self-limited laryngospasm in 3 %, high rate of  | Study was not double-blinded                   | Ketamine starting dose should be at least |
| al[4]        | single-blinded                        | desaturations (approx. in 40%), vomiting in 17%, regardless of        |                                                  | 1 mg/kg; more emergence reactions        |
|              | Patients: N = 201; 1–38 yr          | study group; more emergence reactions in ketamine group during        | without midazolam premedication; same frequency of other adverse reactions |
|              | Procedure: gastroscopy, colonoscopy  | recovery (10 vs 2) Effectiveness: high rate of sedation adequacy      |                                                  |                                          |
|              | Drugs: ketamine (0.75 mg/kg with      |                                                  |                                                  |                                          |
|              | additions of 0.25 mg/kg up. max. to  |                                                  |                                                  |                                          |
|              | 1.5 mg/kg; repeated after 10–15 min  |                                                  |                                                  |                                          |
|              | at 0.5 mg/kg as needed)              |                                                  |                                                  |                                          |
|              | Intervention: midazolam (0.1 mg/kg;  |                                                  |                                                  |                                          |
|              | max 2.5 mg; repeated after 30–60 min |                                                  |                                                  |                                          |
|              | at 0.05 mg/kg as needed)             |                                                  |                                                  |                                          |
|              | Intended sedation level: deep sedation|                                                  |                                                  |                                          |
|              | Additional interventions: none        |                                                  |                                                  |                                          |
|              | Administered by: dedicated nurse     |                                                  |                                                  |                                          |
|              | under supervision of endoscopist     |                                                  |                                                  |                                          |
|              | Outcome measures:                    |                                                  |                                                  |                                          |
|              | Adverse events: respiration rate, HR |                                                  |                                                  |                                          |
|              | BP, SaO2 (any drop below 92%), adverse |                                                  |                                                  |                                          |
|              | reactions                           |                                                  |                                                  |                                          |
|              | Effectiveness: ease of procedure,    |                                                  |                                                  |                                          |
|              | total ketamine consumption           |                                                  |                                                  |                                          |
|              |                                      |                                                  |                                                  |                                          |
| Miqdady et   | Study type: retrospective cohort study| Adverse events: desaturation in 12.5%, in 1.2% disruption of examination due to persistent desaturation; in 1.2% respiratory distress after examination | Retrospective study                            | Midazolam and ketamine sedation is safe and effective for diagnostic GI endoscopies in children older than 1 yr weighting more than 10 kg with comorbidities |
| al[5]        | Patients: N = 301; 1 (more than 10 kg)–18 yr; ASA 1, II |                                                  |                                                  |                                          |
|              | Procedure: upper, lower or combined  |                                                  |                                                  |                                          |
|              | GI endoscopy                         |                                                  |                                                  |                                          |
|              | Drugs: atropine (0.01-0.02 mg/kg per |                                                  |                                                  |                                          |
|              | minute; 0.1 mg max. 0.4 mg); midazolam (0.05-0.2 mg/kg); ketamine (0.5–1 mg/kg) |                                                  |                                                  |                                          |
|              | Intended sedation level: deep sedation|                                                  |                                                  |                                          |
|              | Additional interventions: none        |                                                  |                                                  |                                          |
|              | Administered by: endoscopist         |                                                  |                                                  |                                          |
|              | Outcome measures:                    |                                                  |                                                  |                                          |
|              | Adverse events: respiration rate, HR, |                                                  |                                                  |                                          |
|              | BP, SaO2 (any drop below 94%), side  |                                                  |                                                  |                                          |
|              | effects                              |                                                  |                                                  |                                          |
|              | Effectiveness: the adequacy of        |                                                  |                                                  |                                          |
|              | sedation                            |                                                  |                                                  |                                          |
Motamed et al\[6\]

Study type: prospective, randomised, double-blinded

Patients: N = 150; 1–18 yr; ASA 1, II

Procedure: upper GI endoscopy

Drugs: main sedative: midazolam 0.1 mg/kg if needed repeated doses up to 5 mg or 0.3 mg/kg; premedication 45 min before the procedure with oral placebo (normal saline), oral ketamine (5 mg/kg), or oral fentanyl (2 μg/kg)

Additional interventions: spray of lidocaine 10%; additional oxygen through nasal cannula at 2 L/min

Administered by: registered nurse supervised by anaesthesiologist

Outcome measures:

Adverse events:

- Sedation with oral ketamine-iv midazolam is better than placebo-midazolam or oral fentanyl-iv midazolam

Effectiveness:

- the total recovery and procedure duration time was shorter in the ketamine-midazolam group, inadequate sedation in 10.2%

Long et al\[9\]

Study type: retrospective analysis of prospectively collected data

Patients: N = 4904; 15–90 yr; ASA 1–IV

Procedure: esophagogastroduodenoscopy

Drugs: propofol 1–100 mg and/or midazolam 1–3 mg/kg

Administered by: endoscopist

Outcome measures:

- influence of pre-existing disease and ASA score on oxygen desaturation (SpO₂) < 90%

Chiaretti et al\[7\]

Study type: retrospective (12 yr), multicentric

Patients: N = 36516; 1 to > 10 yr; ASA I, II, III

Procedure: different painful procedures

Drugs: main sedative: propofol 2 mg/kg in children from 1 to 8 yr of age and 1 mg/kg in older children and in children younger than 1 yr; further doses of 0.5–1.0 mg/kg in the case of agitation or complaint; premedication: atropine 0.001–0.015 mg/kg, ketamine (0.5 mg/kg) to avoid infusion pain in 2 centres (not in gastroscopy); additional oxygen through nasal cannula at 6 L/min

Intended sedation level: deep sedation

Administered by: paediatrician (anaesthesiologist available in case of need)

Outcome measures: mean arterial pressure, heart rate and SatO₂, incidence, type and timing of adverse events (major and minor) and number of calls to the emergency team

Effectiveness: total dose of the sedative agents, level of sedation (Ramsay scale)

Gül et al\[8\]

Study type: randomized, controlled, double-blinded

Patients: N = 64; 3–14 yr; ASA I

Procedure: esophagogastroduodenoscopy

Drugs: main sedative: propofol 2 mg/kg analgesic: group R: remifentanil 0.25 μg/kg; group F: fentanyl 0.5 μg/kg; additional oxygen through nasal cannula at 4 L/min

Intended sedation level: deep sedation

Administered by: anesthesiologist

Outcome measures: MAP, HR, RR, and SpO₂ consumption, and duration of recovery were significantly shorter in group R

Effectiveness: ease of gastroscopy, patient’s movements during procedure, additional doses of drugs; level of sedation (Ramsay scale); duration of PACU stay

Adverse events:

- prolonged apnoea in 14 (43.8%) children in group R and in 11 (33.3%) children in group F; none required endotracheal intubation; intraoperative respiratory rate, time to eye opening, opioid consumption, and duration of recovery were significantly shorter in group R than in group F

Remifentanil (combined with propofol) is an efficient and as safe as fentanyl propofol combination for esophagogastr duodenoscopy in children

Retrospective study

Propofol is safe and effective for paediatrician-administered procedural sedation in children; appropriate training for paediatricians is important

Orel R et al.

Sedation with oral ketamine-iv midazolam is better than placebo-midazolam or oral fentanyl-iv midazolam

Retrospective study

Independent risk factors for hypoxemia were high BMI, hypertension, diabetes, gastrointestinal and heart diseases and combined gastro and colonoscopy
English which addressed different aspects including sedation [12].

We expanded the search to guidelines for sedation for GI endoscopy performed by non-anesthesiologists in adult patients during the last 10 years. The search revealed 9 publications which are listed in Table 2[16-24].

The search for guidelines for pediatric procedural sedation published in English during the last 10 years revealed 10 publications. Two are general guidelines for sedation in children [25,26]. Another one, followed by an update published 7 years later, addresses specifically ketamine sedation for emergency departments [27,28]. Others are specifically developed for sedation for dental procedures in children. They are listed in Table 3 [15,25,26,28-33].

Pre-requisites for safe and effective sedation by non-anesthesiologists

GI endoscopy must be discussed with the child if emotionally and intellectually competent enough and parent(s)/guardian(s). The pre-sedation assessment is listed in Table 4. Patients should be classified by physical status assessment as developed by the American Society for Anesthesiology (ASA) (Table 5). If the child's ASA classification conforms to class I or II, sedation can be performed safely. If the child fits in ASA class III classification, the benefits of sedation must be carefully weighed against the risks and in the vast majority of cases anesthesia will be preferable. Patients in ASA class IV and V must be anesthetized by anesthesiologists [28,31].

The depth of sedation is influenced by the procedure. If analgesia is needed together with sedation, as in the case of endoscopic-therapeutic procedures, the patient has to be anesthetized. The same is valid for emergency GI endoscopies such as removal of a foreign body from the upper GI tract and GI bleeding. Sedation necessitates that a team member assigned for observing the vital signs of the patient, since monitoring of pulse oximetry, heart rate and preferably also capnography are insufficient [8,12].

Equipment for resuscitation must be present in the endoscopy room. The team has to be trained in pediatric advanced life support techniques and has to be familiar with measures needed in any scenario of complications [3].

Sedatives and their combinations

Legislation and regulation regarding limitations of administration of different medications, such as inhalation anesthetics, differ from country to country. Therefore, limitations caused by local legislation should be carefully checked. In most countries, the administration of inhalation anesthetics is only authorized by anesthesiologists.

Premedication

Premedication with midazolam (oral or intra-nasal) lessens the stress for an intravenous (iv) catheter placement and other preparations for GI endoscopy before sedation or anesthesia. This procedure is effective and safe although intranasal administration may cause local discomfort. In order to decrease the stress and pain caused by a venipuncture, an eutectic mixture of the topical anesthetics lidocaine and prilocaine provides local anesthesia when applied with an occlusive dressing 30-60 min before venipuncture [8].

An iv catheter provides the most effective way of delivering agents needed for sedation and analgesia. Inhalation, intramuscular or other sedation regimens are less well
### Table 2  Gastrointestinal endoscopy sedation guidelines for adults

| Organisation Ref. | Title | Year of publication |
|-------------------|-------|---------------------|
| American Association for the Study of Liver Diseases; American College of Gastroenterology; American Gastroenterological Association Institute; American Society for Gastrointestinal Endoscopy; Society for Gastroenterology Nurses and Associates | Multisociety sedation curriculum for GI endoscopy | 2012 |
| Vargo et al[16] | Task Force Members. European Society of Gastrointestinal Endoscopy, European Society of Gastroenterology and Endoscopy Nurses and Associates, and the European Society of Anaesthesiology | Guideline: Non-anesthesiologist administration of propofol for GI endoscopy | 2010 |
| Dumonceau et al[17] | Society of American Gastrointestinal Endoscopic Surgeons | Surgeons. Society of American Gastrointestinal Endoscopic Surgeons guidelines for office endoscopic services | 2009 |
| Heneghan et al[18] | Standards Practice Committee of the American Society for Gastrointestinal Endoscopy | Sedation and anesthesia in GI endoscopy | 2008 |
| Lichtenstein et al[19] | Training Committee of the American Society for Gastrointestinal Endoscopy | Training in patient monitoring and sedation and analgesia | 2007 |
| Vargo et al[20] | Working Group on Endoscopy, Austrian Society of Gastroenterology and Hepatology (OGGH) | Austrian Society of Gastroenterology and Hepatology (OGGH)-guidelines on sedation and monitoring during GI endoscopy | 2007 |
| Schreiber[21] | Training Committee | Training guideline for use of propofol in gastrointestinal endoscopy | 2004 |
| Dumonceau et al[22] | American Society for Gastrointestinal Endoscopy, Standards of Practice Committee | Guidelines for conscious sedation and monitoring during GI endoscopy | 2003 |
| Waring et al[23] | Standards Practice Committee | Guidelines for the use of deep sedation and anesthesia for GI endoscopy | 2002 |

**GI:** Gastrointestinal.

### Table 3  Paediatric procedural sedation guidelines

| Organisation Ref. | Title | Year of publication |
|-------------------|-------|---------------------|
| Green et al[26] | Clinical practice guideline for emergency department ketamine dissociative sedation: 2011 update | 2011 |
| National Clinical Guideline Centre (United Kingdom)[27] | Sedation in children and young people: Sedation for diagnostic and therapeutic procedures in children and young people | 2010 |
| American Academy on Pediatric Dentistry Clinical Affairs Committee-Sedation and General Anesthesia Subcommittee; American Academy on Pediatric Dentistry Council on Clinical Affairs | Guideline on use of anesthetics personnel in the administration of office-based sedation/general anesthesia to the pediatric dental patient | 2009 |
| American Academy on Pediatrics; American Academy on Pediatric Dentistry[28] | Guideline for monitoring and management of pediatric patients during and after sedation for diagnostic and therapeutic procedures | 2009 |
| American Academy on Pediatrics; American Academy of Pediatric Dentistry | Guidelines for monitoring and management of pediatric patients during and after sedation for diagnostic and therapeutic procedures: an update | 2006 |
| Coté et al[29] | American Academy on Pediatric Dentistry Clinical Affairs Committee-Sedation and General Anesthesia Subcommittee; American Academy on Pediatric Dentistry Council on Clinical Affairs[30] | Guideline on use of anesthesia care providers in the administration of in-office deep sedation/general anesthesia to the pediatric dental patient | 2005 |
| American Academy on Pediatric Dentistry | Guideline on the elective use of minimal, moderate, and deep sedation and general anesthesia for pediatric dental patients | 2005 |
| American Academy on Pediatric Dentistry Committee on Sedation and Anesthesia[31] | American Academy of Pediatric Dentistry[32] | Clinical guideline on the elective use of minimal, moderate, and deep sedation and general anesthesia for pediatric dental patients | 2004 |
| Green et al[33,28] | Clinical practice guideline for emergency department ketamine dissociative sedation in children | 2004 |
| UK National Clinical Guidelines in Pediatric Dentistry Hosey[34] | UK National Clinical Guidelines in Paediatric Dentistry. Managing anxious children: the use of conscious sedation in paediatric dentistry | 2002 |
An iv catheter is also important for emergency access in the case of adverse events occurring during sedation or the endoscopic procedure\cite{25,36,37}.

Mechanisms of action and the main undesirable effects of sedatives and adjuvant medicines are listed in Table 6\cite{8,38-49}. Usual dosage regimens and the main contraindications are listed in Table 7.

**Propofol**

Propofol is a rapid onset and short acting anesthetic without analgesic properties and with a narrow therapeutic range. Its sedative properties result from agonistic action on gamma-aminobutyric acid (GABA) receptors. Propofol is contraindicated in infants younger than 1 mo because of missing data on safety according to a Cochrane review\cite{50}. The main undesirable effects include pain on injection, respiratory depression, bradycardia and hypotension\cite{38,46}.

van Beek and Leroy\cite{2} reported failure to conduct a procedure due to incomplete sedation in only 0.0%–0.4% of cases, despite the fact that the sedation was performed in 88.1% by non-anesthesiologists\cite{2}. The recovery time after propofol administration was shorter than after midazolam/meperidine\cite{2}. Major respiratory complications occurred in 11/3883 propofol sedations (0.3%), but no intubation and no sequelae were reported. The incidence of undesirable effects (e.g., temporary desaturation due to hypoventilation, laryngospasm) was comparable to other protocols and was more frequent in younger children, especially infants\cite{2}.

A randomized study in 90 adults undergoing colonoscopy showed that the satisfaction of patients was greater...
and there were less undesirable effects when they were sedated by an endoscopist than by an anesthesiologist\footnote{51}. A Scandinavian study tested a 6-wk educational program for registered nurses with excellent safety results\footnote{52}.

The largest multicenter prospective study of propofol sedation for different pediatric procedures outside an operating theatre was published by the international (United States and Canada) Pediatric Sedation Research Consortium. They analysed the data of 49836 propofol sedation episodes and showed that propofol-based sedation is amongst the safest sedation practice for children\footnote{53}. Cardio-respiratory resuscitation was necessary in two cases. Pulmonary aspiration of gastric fluid secondary to vomiting during sedation occurred in four patients. Less serious respiratory adverse events were: desaturation in 154/10000 procedures; central apnea or upper airway obstruction in 124/10000; stridor in 10/10000; laryngospasm in 20/10000; excessive salivation in 73/10000; and vomiting in 10/10000 cases. The authors of this report estimate propofol sedation for children is only to be considered when anesthetic teams are not motivated and well organized sedation/anesthesia teams, and that priority should go to actions to obtain these anesthetic teams.

Chiaretti et al\footnote{7} published a retrospective study on pediatric procedural sedation with propofol over a 12-year period in three Italian hospitals\footnote{7}. They analyzed 36516 procedural sedations for different painful procedures. Deep sedation was achieved in all patients. None of the children experienced severe side effects or needed a prolonged hospitalization. In six patients (0.02%) emergency team had to intervene (prolonged laryngospasm in three patients, bleeding in one, intestinal perforation in one, and one during lumbar puncture). But milder adverse events were more often: hypotension in 19 patients (0.05%), ventilation by face mask and additional oxygen in 128 patients (0.4%), laryngospasm in 78 patients (0.2%), bronchospasm in 15 patients (0.04%). Minor complications were more often in children who underwent gastroscopy.

The usual loading dose of propofol is 2 mg/kg in infants and young children (younger than 3 years) and 1 mg/kg in older children and teenagers. Subsequent
| Medicine generic name | Route | Dose | Time to start sedation/analgesia (after iv application) | Sedation/analgesia duration | Repeating time and dose | Contraindications | Comments | Ref. |
|-----------------------|-------|------|------------------------------------------------|-----------------------------|------------------------|---------------------|----------|------|
| Fentanyl              | iv    | 1–2 μg/kg (up to 50 μg) | 0.5 s | 20–40 min (30–60 min) | 3 min 1–1.25 μg/kg | 10 min 0.5 μg/kg | Severe cardiovascular disease, malignant hypertension, CSF obstructive states (controversial), intracranial pressure pathology; previous psychiatric illness, hyperthyroidism or thyroid medicine use; porphyria | Due to higher clearance younger children need frequent dosing. A single enantiomer S(+); the anesthetic management of seriously ill hypovolemic patients, it may be the agent of choice for managing children and burned patients; low cost | [38,40] |
| Ketamine              | iv slowly over 1 min; other routes have less predictive effects and different dosing – see the discussion | 1–1.5 mg/kg | 1–5 min | 15 min | Repeating every 2–5 min until desired effect; in children 6 mo–5 yr total dose up to 0.6 mg/kg or max. 6 mg; in 6–12 yr total dose up to 0.4 mg/kg or max. 10 mg; in older than 12 yr additional boluses of 1 mg until desired sedation | Respiratory depression, hypotension | Simultaneous treatment with monoamine oxidase inhibitors | Rarely used as a sole sedative; might be used to sedate the frightened child before iv catheter placement; mostly combined with opioids; paradoxical irritation in 1%–5% of patients | [38,40–42] |
| Meperidine            | iv slowly over 1–2 min | 0.3–2 mg/kg | 3–6 min | 60–180 min | Repeating every 2–5 min until desired effect; in children 6 mo–5 yr total dose up to 0.6 mg/kg or max. 6 mg; in 6–12 yr total dose up to 0.4 mg/kg or max. 10 mg; in older than 12 yr additional boluses of 1 mg until desired sedation | Respiratory depression, hypotension | Simultaneous treatment with monoamine oxidase inhibitors | Rarely used as a sole sedative; might be used to sedate the frightened child before iv catheter placement; mostly combined with opioids; paradoxical irritation in 1%–5% of patients | [38,40] |
| Midazolam             | iv slowly over 2–3 min; other routes have less predictive effects and different dosing | 0.05–0.1 mg/kg in < 5 yr (max. 0.6 mg/kg); in 6–12 yr 0.025–0.05 mg/kg (max. 0.4 mg/kg); in older than 12 yr 2–2.5 mg (in total not more than 2 mg/kg BW) | 2–3 min | 45–60 min | Repeating every 2–5 min until desired effect; in children 6 mo–5 yr total dose up to 0.6 mg/kg or max. 6 mg; in 6–12 yr total dose up to 0.4 mg/kg or max. 10 mg; in older than 12 yr additional boluses of 1 mg until desired sedation | Respiratory depression, hypotension | Simultaneous treatment with monoamine oxidase inhibitors | Rarely used as a sole sedative; might be used to sedate the frightened child before iv catheter placement; mostly combined with opioids; paradoxical irritation in 1%–5% of patients | [38,40] |
| Nitrous oxide         | Inhalation | Mostly the mixture of nitrous oxide (90%) and oxygen | 0.5–1 min | 5 min | Continuously or “on demand” | Respiratory depression, hypotension | Pneumothorax, bowel obstruction, head injury, pregnancy | Simultaneous treatment with monoamine oxidase inhibitors | [38,40,45] |
| Propofol              | iv    | 2 mg/kg in infants and young children (younger than 3 yr); 1 mg/kg in children older than 3 yr | 1–2 min | 5–15 min | 1 mg/kg (infants and children up to 3 yr); 0.5 mg/kg (children older than 3 yr) to reach the desired sedation; may be continuously infused at 100 μg/kg per min and increasing the speed of infusion by 50 μg/kg per min for prolonged procedures | Egg or soy allergy | Egg or soy allergy | For additional medication to alleviate infusion pain see text; alfentanil but not fentanyl increases propofol blood level; in many countries the use is limited to anaesthesiologists | [38,40,46] |
| Sevoflurane           | Inhalation | Different concentrations according to the age | | | | Duchenne’s muscular dystrophy, moderate to severe liver disease of unknown aetiology, history of malignant hyperthermia | Duchenne’s muscular dystrophy, moderate to severe liver disease of unknown aetiology, history of malignant hyperthermia | Due to its shorter duration of action than most of opioids (e.g., fentanyl) repeated doses may be needed | [47–49] |
| Antagonists           |       |       |       |       |       |       |       |       |
| Flumazenil           | iv    | 0.02 mg/kg (max. 1 mg) | 1–3 min | 30 min | 1 min; same dose | Chronic benzodiazepine use; ingestion of drugs that increase the risk for seizures development (e.g., cyclic antidepressants, cyclosporine, and others) | Due to its shorter duration of action than most of benzodiazepines (e.g., midazolam) repeated doses may be needed | [38,40] |
| Naloxone             | iv or i.m. | 0.1 mg/kg (max. 2 mg) | 2 min | 20–40 min | 2 min; same dose | Hyperosensitivity only | Hyperosensitivity only | Due to its shorter duration of action than most of opioids (e.g., fentanyl) repeated doses may be needed | [38,40] |
boluses of 1 mg/kg for younger, or 0.5 mg/kg for older children, may be added to ensure the appropriate level of sedation. For longer procedures propofol may be administered in a continuous infusion[38].

For painful procedures an analgesic must be added as propofol has no analgesic properties[38]. Bedirli et al[30] showed that the addition of tramadol or fentanyl to propofol provided efficient sedation, with less adverse events in the tramadol group (less desaturation, hypotension, and bradycardia; but more vomiting in fentanyl group)[31]. According to Gül et al[30] there was no difference in safety and efficacy between remifentanil and fentanyl co-administration with propofol.

The pain of propofol injection can be reduced by choosing a larger vein such as the antecubital site, or alternatively the injection of lidocaine[54]. A possible flow chart of propofol sedation for pediatric GI endoscopy is presented in Figure 1.

Generally, one cannot extrapolate data from adult practice to children. However, four different European Societies (of Gastrointestinal Endoscopy, of Gastroenterology, of Endoscopy Nurses and Associates, and of Anesthesiology) jointly issued guidelines for propofol sedation of adults for GI endoscopy by non-anesthesiologists[16]. It is interesting that although the Board of Directors of the European Society of Anesthesiology (ESA) decided unanimously to endorse these guidelines, a majority of the national societies of the ESA did not support them. Consequently ESA retracted the endorsement[55]. The Danish training program for nurses includes training on how to administer propofol for GI endoscopic procedures in adults[52].

Ketamine
Ketamine is a dissociative anesthetic and analgesic. It is an N-methyl-D-aspartate channel antagonist and

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**Figure 1** Flow chart of propofol sedation protocol for paediatric gastrointestinal endoscopy. 1Older than 1 mo, without contraindications (egg or soy allergy); 2Diagnostic endoscopy or procedure for which no endotracheal intubation is needed; 3The team qualified for paediatric sedation for gastrointestinal endoscopy.
depresses sensory association areas of the cortex, limbic system and thalamus. It has been used for a long time for sedation and analgesia in emergency pediatrics due to its association with a preserve gag reflex and lack of respiration depression and hypotension. Despite its good safety profile, the significant association with laryngospasm (especially with gastroscopy), emergence phenomena such as hallucinations, excitation, nightmares, delirium, recurrent illusions or “flashbacks”, vomiting, and hypersalivation limit ketamine’s broader use.

When used as a sedative, ketamine must be administered by slow iv injection at a dosage of 1-2 mg/kg initially. The sedative effect lasts 10-15 min. Repeated doses of 0.5 mg/kg prolong its action (Figure 2).

The most frequent undesirable effects are vomiting, hypersalivation, nystagmus, hypertension, tachycardia, skin erythema, and emergence phenomena. Laryngospasm, which is potentially of greatest danger, is uncommon. The use of ketamine is contraindicated in infants younger than 3 mo, patients with psychosis, uncontrollable hypertension or hyperthyroidism, and as it increases intracranial and intraocular pressure. Ketamine should not be used after a head or eye trauma, or surgery, although some data advocate against these precautions.

The concomitant use of midazolam with ketamine decreases the frequency of emergence phenomena, although this remains controversial. Two randomized double-blind studies performed in pediatric emergency departments did not find sufficient evidence to support the addition of midazolam for this purpose. However, a randomized study using midazolam in co-administration with ketamine for pediatric sedation for GI endoscopy

Figure 2 Flow chart of ketamine sedation protocol for paediatric gastrointestinal endoscopy. 1Older than 3 mo, without contraindications (severe cardiovascular disease, malignant hypertension, CSF obstructive states, intracranial pressure pathology, psychotic illness, hyperthyroidism or thyroid medicines use, and porphyria); 2Diagnostic endoscopy or procedure for which no endotracheal intubation is needed; 3The team qualified for paediatric sedation for gastrointestinal endoscopy.
suggests that midazolam does prevent emergence phenomena. Other co-administered medicines might lessen some undesirable effects of ketamine but their use is not supported by sufficient evidence. Anticholinergics may prevent hypersalivation, but this has also been contradicted. The anti-emetic ondansetron prevents vomiting in some patients.

**Benzodiazepines and opioids**

Midazolam is a short-acting benzodiazepine which is widely used for sedation but is generally considered to be insufficient as a monotherapy. It has anxiolytic, amnesic, sedative, hypnotic, muscle relaxant, and anticonvulsant properties which result from GABA receptor activation. The major undesirable effects are respiratory depression and hypotension, which are avoidable with appropriate dosing and are reversed by the antagonist flumazenil. Other undesirable effects such as paradoxical agitation are reported in up to 15% of children.

Midazolam may be administered orally as an anxiolytic before the placement of an IV cannula but its effect is less predictive orally than when administered IV. The usual starting dose is 0.1 mg/kg IV as a pre-medication but may be titrated to the desired effect by incremental doses of 0.05 mg/kg.

Opioids are potent analgesics which express their activity via different opioid receptors. The most suitable for sedation is fentanyl due to its rapid onset and short action. As it has no sedation properties, it must be combined with benzodiazepines but the combination increases the risk of respiratory depression. Other undesirable effects are itching, hypotension, and vomiting, but those are less pronounced than in histamine-releasing opioids such as morphine and meperidine. Naloxone is an opioid receptor antagonist and is administered intravenously at 0.1 mg/kg.

Meperidine was the first synthetic opioid agent. It acts mainly as an antagonist of μ and K receptors and has an analgesic potency ten times greater than that of morphine. Like other opioid drugs, meperidine causes nausea, vomiting, urinary retention and respiratory depression. Its property of acting on nerve fibers, similar to those of local anesthetics, allows its use as an alternative for anesthetic blockade and differentiates it from other opioids. An IV route has been used for treating moderate to severe pain, for regional anesthesia, for pre-medication and for analgesia during anesthesia. The combination of midazolam and meperidine can be used to achieve sedation and analgesia during colonoscopy. There are few studies that have compared the efficacy of midazolam alone to midazolam and meperidine. According to Ozel et al., there were no significant differences in oxygen saturation/blood pressure but a better patient compliance was observed in the combined sedation group. Cinar et al. showed that in respect of the recovery and procedure time there were no significant differences between the midazolam and the midazolam/meperidine group. In a randomized trial comparing the efficacy and recovery time of two sedation regimens consisting of midazolam in combination with either meperidine or fentanyl, it was found that the fentanyl combination with midazolam resulted in a significantly faster recovery, without any apparent loss of analgesic effect. Again, these are adult studies, and extrapolation to pediatrics is not necessarily appropriate.

Meperidine is administered intravenously at 1 mg/kg. A possible flow chart of benzodiazepine and opioid sedation for pediatric GI endoscopy is presented in Figure 3.

Fentanyl is usually administered at 1–2 μg/kg. The analgesic effect lasts 20–40 min.

van Beek and Leroy’s analysis found opioid and benzodiazepine sedation protocols suboptimal. These protocols were inferior in comparison to general anesthesia. The comparison of midazolam/fentanyl with propofol sedation by Lightdale et al. addressed mainly procedure duration and discharge times which were similar for both groups, but the endpoint of this study was not to compare safety or efficacy.

**Inhalation anesthetics**

In most countries, legislation limits the administration of inhalation anesthetics to anesthesiologists.

**Sevoflurane:** Sevoflurane is an inhalational anesthetic with a very good safety profile (low incidence of airway hypersecretion, respiratory depression or cardiovascular events). When used for paediatric sedation for endoscopies it was characterized by a shorter recovery time and earlier discharge. Sevoflurane can only be administered by an anesthesiologist. The insertion of an IV catheter may not be needed. The use of inhaled anesthetics requires waste gas scavenging to prevent anesthetic gases being released into the ambient air.

There are no recently published studies on sevoflurane sedation for pediatric GI endoscopies.

**Nitrous oxide:** Nitrous oxide is an inert gas which has analgesic, sedative and amnesic properties of short duration. Michaud et al. reported a good experience with 50% nitrous oxide for gastroscopies and proctosigmoidoscopies in children. They did not evaluate it for ileo-colonoscopy nor compare this type of sedation to other protocols. There are no newer studies on nitrous oxide sedation for GI endoscopy in children.

In adults nitrous oxide has been used successfully for proctoscopies and colonoscopies. In a systematic review Welchman et al. analyzed a systematic review 11 studies including 623 patients. Continuous nitrous oxide inhalation provided comparable analgesia to IV sedation for colonoscopies. There was no difference in procedural pain between on-demand nitrous oxide and no sedation for colonoscopies. The recovery time was shorter in the nitrous oxide groups.

Nitrous oxide is often more used as an anxiolytic before IV catheter placement if the face mask does not agitate the patient. However, most anesthesiologists...
would suggest that age-appropriate calming of a patient by engagement would have a similar result. Vomiting occurs in up to 10%. It is contraindicated in bowel obstruction and should not be administered if any of the team members is pregnant. Its routine use in pediatric GI endoscopy is not ratified.

**Adjuvant medicines and antagonists**

**Anti-cholinergics:** As discussed in the section on ketamine, anti-cholinergics (e.g., atropine or glycopyrrolate) decrease the hypersalivatory effect which may influence airway patency. However, importantly, it should be noted that available evidence does not support this practice and anti-cholinergics are no longer routinely recommended.

**Anti-emetics:** Many sedative/analgesic agents (e.g., ketamin, fentanyl), with the exception of propofol, provoke vomiting. Ondansetron reduced the incidence of vomiting in a double-blind, randomized, placebo-controlled study in 255 children in an emergency department sedated by ketamine.

**Flumazenil:** Flumazenil is an antagonist used to reverse the undesirable effects of benzodiazepines such as respiratory depression. It is delivered iv at 0.1 mg/kg up to a maximum of 2 mg and has a rapid onset of action in 1-3 min. The half-life of flumazenil is shorter than that of other benzodiazepines (e.g., midazolam) making close monitoring essential and reapplication sometimes needed.

**Naloxone:** Naloxone reverses opioid effects and results in normal respiration within 1-2 min of application of 0.1 mg/kg (up to 2 mg) iv or intramuscular. Its duration of action is around 20-40 min hence repeated doses might be needed as the duration of action of most opioids (e.g., fentanyl) is longer.

**DISCUSSION**

Effective and safe sedation for pediatric endoscopic proce-
dures is a non-negotiable pre-requisite and an important factor for lowering patient distress. In principle, total iv anesthesia should be performed by anesthesiologists. However, it has to be recognized that in many countries, including a majority of European countries and in parts of the United States, the limited availability of anesthesiology teams and limited organizational considerations represents a medical dilemma. In many European countries anesthesia departments cannot cope with the increasing demands[27]. Therefore, a shortage of anesthetic teams may force pediatric endoscopists to conduct sedation without anesthetic teams applying guidelines adapted according to national regulations and institutional practices[41]. However, this situation is not optimal and requires consequent actions to increase the number of anesthesiologists.

In this situation, the intention of the authors is not to encourage such practice. This paper summarizes the evidence for sedation schemes which could be safely and efficiently performed by non-anesthesiologists. Sedation protocols have to be adapted to international, national and local legislation and institutional practice. The national institutions must organize multidisciplinary teams for education, licensing and supervision of non-anesthesiologists and registered nurses involved in sedation practices as long as there is a shortage of anesthesiologists. An efficient system of quality control is a paramount.

The choice of medicines for procedural sedation is wide, but none has the properties of an ideal sedative, which are: predictable dose dependent level of sedation with rapid onset; broad therapeutic window; anxiolytic effect with anterograde amnesia for the duration of the procedure; absence of respiratory, cardiovascular and other undesirable effects; and a smooth post-procedural recovery without side effects[34]. Another important problem in pediatrics is the off-label use of many medicines, which was recently addressed for medicines prescribed for outpatients in pediatric gastroenterology[39]. The investigators found that in 33.2% of the prescriptions, medicines were used “off-label” and that 47.3% of the patients had at least 1 medicine described as an “off-label” medication. Sedatives and other iv medicines were not covered by this study. The legal risk of a prescribing doctor is greater when using “off-label” medicines or indications. Parents should be informed of the “off-label” use. A solution of this problem is to motivate the pharmaceutical companies to register medicines for pediatric use, as has happened in the majority of the EU Countries under the jurisdiction of the European Medical Agency for new medicines.

Propofol is probably the most promising and controversial sedative/anesthetic at present. It is stated that only those trained in anesthesia should use it, a position that anesthesiologists and their societies strongly defend[30]. On the other hand, there are studies of safe and efficient use of propofol for sedation for GI endoscopic investigations in pediatric and adult gastroenterology[2,3,7,8,51,71]. The administration of propofol by non-anesthesiologists is “off-label” in most cases and, therefore, every adverse event might have medico-legal consequences.

Therefore, these data could not be simply extrapolated to every sedation/analgescis practice. According to the review by Havidich et al[22] the evidence of the safety of sedation by non-anesthesiologists for procedures outside operating theatres is growing, especially for propofol. Despite the drawbacks listed above, published data justify propofol use in certain circumstances[22].

Ketamine-based sedation is safe and effective in otherwise healthy infants older than 3 mo[27]. Ketamine has dissociative anesthetic and analgesic properties with a wide safety margin and is frequently used in pediatric emergency departments[27,28]. Emergence reactions are observed in adults in up to 28%, but seem less prevalent in paediatric studies and not influenced by the addition of midazolam to ketamine[56-58]. Guidelines advised against routine benzodiazepine pre-medication[27,28]. Data from larger studies are needed as one recent study found less emergence reactions when midazolam was routinely administered as a pre-medication[41]. Another major limitation of ketamine-based sedation for endoscopy is laryngospasm. In general, the laryngospasm resolves without consequences rapidly after removal of the endoscope and administration of oxygen[73]. Another study reports transient laryngospasm manageable with simple measures in 3% of gastroscopies[4]. Therefore, the ketamine-based sedation regime for GI endoscopy is an acceptable option when sedation with propofol is not feasible.

Midazolam is most likely the most widely used drug for sedation in everyday endoscopic work. The duration of action of midazolam is dependent on the duration of its administration. The sedative and amnestic effects of benzodiazepines sometimes do not provide adequate patient comfort during colonoscopic procedures[74]. Opioids are often added and meperidine is commonly used[55]. The value of adding analgesics to sedatives has well evaluated in large number of prospective, randomized and placebo-controlled studies[56]. Sedation with midazolam/meperidine is safely and can be administrated under adequate monitoring[77].

These recommendations review and discuss sedation practices for pediatric GI endoscopy which can be safely and efficiently performed by non-anesthesiologists, but only when the necessary pre-requisites regarding patient assessment, team composition and experience, medicines and equipment are met.

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The authors reviewed the literature and made practical recommendations for effective and safe sedation for endoscopic procedures in children. However, the authors decline every legal responsibility for the proposed algorithms. Legislation and regulation regarding limitations of administration of different medications, such as inhalation anesthetics, differ from country to country.
Therefore, limitations caused by local legislation should be carefully checked.

COMMENTS

Background

Anesthesia is by preference performed by anesthesiologists.

Research frontiers

The creation of sedation teams led by non-anesthesiologists and a careful selection of anesthetic drugs may offer an alternative, but should be in line with national legislation and institutional regulations.

Innovations and breakthroughs

The intention of this review is to offer effective and safe alternatives for non-anesthesiologists.

Peer-review

The present paper was well organized and well investigated. This paper will give us important information about the anesthesia during endoscopy especially in children.

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