Accepted: 25 February 2018

DOI: 10.1111/pan.13365

RESEARCH REPORT

WILEY Pediatric Anesthesia

The impact of Narcotrend™ EEG-guided propofol administration on the speed of recovery from pediatric procedural sedation—A randomized controlled trial

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Funding information
This study was supported by a grant of the faculty of medicine of the Erasmus University Rotterdam, The Netherlands.

Section Editor: Dean Kurth

Summary

Background: Propofol is often used for procedural sedation in children undergoing gastrointestinal endoscopy. Reliable assessment of the depth of hypnosis during the endoscopic procedure is challenging. Processed electroencephalography using the Narcotrend Index can help titrating propofol to a predefined sedation level.

Aims: The aim of this trial was to investigate the impact of Narcotrend Index-guided titration of propofol delivery on the speed of recovery.

Methods: Children, aged 12-17 years, undergoing gastrointestinal endoscopy under procedural sedation, had propofol delivered via target controlled infusion either based on Narcotrend Index guidance (group NI) or standard clinical parameters (group C). Sedation was augmented with remifentanil in both study groups. The primary endpoint of this study was to compare the speed of fulfilling discharge criteria from the operating room between study groups. Major secondary endpoints were propofol consumption, discharge readiness from the recovery room, hypnotic depth as measured by the Narcotrend Index, and adverse events.

Results: Of the 40 children included, data were obtainable from 37. The time until discharge readiness from the operating room was shorter in group NI than in group C, with a difference between medians of 4.76 minutes [95%CI 2.6 to 7.4 minutes]. The same accounts for recovery room discharge times; difference between medians 4.03 minutes [95%CI 0.81 to 7.61 minutes]. Propofol consumption and the percentage of EEG traces indicating oversedation were higher in group C than in group NI. There were no significant adverse events in either study group.

Conclusion: Narcotrend Index guidance of propofol delivery for deep sedation in children aged 12-17 years, underdoing gastrointestinal endoscopy results in faster recovery, less drug consumption, and fewer episodes of oversedation than dosing propofol according to clinical surrogate parameters of depth of hypnosis. The results of this study provide additional evidence in favor of the safety profile of propofol/remifentanil for procedural sedation in adequately selected pediatric patients.

KEYWORDS
child, deep sedation, electroencephalography, endoscopy, gastrointestinal, hypnosis, propofol

1 | INTRODUCTION

Gastrointestinal endoscopy in pediatric patients can be performed either under general anesthesia or procedural sedation and analgesia. When performed under procedural sedation and analgesia, deep sedation [1] is required, which is often indistinguishable from minimal anesthesia,[2] because assessment of depth of hypnosis and titration of hypnotic drugs to a precisely predefined endpoint remain challenging.[3]

Procedural sedation for pediatric gastrointestinal endoscopy using a continuous infusion of propofol can be regarded as safe and effective, as long as sedation is given by sufficiently trained healthcare providers and in carefully selected patients.[4-6] The addition of low-dose continuous remifentanil to provide analgesia and augment propofol effect can be considered effective and safe.[7,8]

Delivering deep sedation or minimal anesthesia to a child with an unsecured airway requires an exceptional high level of situational awareness on the side of the pediatric anesthesiologist. Objective measures of hypnotic depth can provide the anesthesiologist with important information regarding hypnotic drug effect, ultimately leading to improved patient safety.

Electroencephalographic Narcotrend™ monitoring has been shown to be a useful tool to assess the depth of hypnosis in pediatric patients receiving procedural sedation for gastrointestinal endoscopy.[9] We hypothesized that Narcotrend™ monitoring can help titrating propofol delivered by target controlled infusion (TCI) to predefined sedation endpoints, ultimately resulting in shorter discharge times from the operating room, while avoiding both awareness with recall and too deep sedation with possible cardiorespiratory compromise.

The primary endpoint of this prospective randomized controlled trial was to compare the speed of recovery from Narcotrend-guided delivery of propofol for pediatric gastrointestinal endoscopy to standard practice using clinical assessment of hypnotic depth. Major secondary endpoints were comparison of total propofol consumption, discharge readiness from the post anesthesia care unit, post hoc comparison of hypnotic depth as measured by Narcotrend, and adverse events.

What is already known about the topic

- Reliable continuous and nondisruptive assessment of the depth of hypnosis during propofol sedation in pediatric patients is challenging.
- Processed electroencephalography using the Narcotrend Index of depth of hypnosis can help titrating propofol to a desired sedation level during pediatric gastrointestinal endoscopy.

What new information this study adds

- Narcotrend Index guidance of propofol delivery results in significantly shorter recovery times, less drug consumption, and fewer episodes of oversedation than standard practice.

2 | MATERIALS AND METHODS

This single center prospective randomized controlled double-blind trial was approved by the IRB of the Erasmus University Medical Center, Rotterdam, The Netherlands (MEC-2013-180; July 11, 2013) and performed in accordance with the Declaration of Helsinki.

The study was registered in the Nederlands Trial Register on May 12, 2014; trial number NTR4593; principle investigator Dr. Frank Weber. Patient inclusion started on May 27, 2014. Written informed consent was obtained from all patients and their parents or legal representatives. This manuscript adheres to the 2010 CONSORT guidelines (see Figure 1).

Pediatric patients aged 12-17 years, scheduled for upper and lower gastrointestinal endoscopy procedures under procedural sedation and analgesia, performed at Erasmus University Medical Center—Sophia Children's Hospital, Rotterdam, The Netherlands, were eligible for inclusion. Allergies to propofol or remifentanil, any contraindication to endoscopy performed under procedural sedation, a body weight of more than 60 kg (limitation of the pediatric propofol TCI model used), chronic use of drugs influencing the electroencephalogram (EEG), and/or opioids and insufficient understanding of the Dutch language were defined as primary exclusion criteria. Patient request or unexpected need for an inhalation induction due to significant difficulties to obtain intravenous access and any procedural events requiring endotracheal intubation were defined as secondary exclusion parameters.

2.1 | Study procedures

Standard sedation monitoring equipment according to departmental standards (ECG, pulse oximetry, noninvasive blood pressure, and qualitative CO_2 sampling via a nasal cannula) was used.

Before initiation of sedation, all study patients were attached to a Narcotrend™ EEG monitor (MT MonitorTechnik GmbH & Co. KG, Bad Bramstedt, Germany) according to the manufacturer's specifications. The Narcotrend records the frontal EEG to calculate a dimensionless index of depth of hypnosis, the Narcotrend Index, ranging from 0 (very deep hypnosis) to 100 (being fully awake). The Narcotrend monitor records the EEG using 3 conventional ECG electrodes and does not require device-specific EEG electrodes.

Narcotrend data were exported as Excel files for subsequent analyses using the EEG Viewer™ software package (Version 1.6, MT MonitorTechnik GmbH & Co. KG, Bad Bramstedt, Germany).

Propofol was administered using the Paedfusor TCI model [10] on an Alaris™ PK Syringe Pump (CareFusion UK 306 Ltd, Basingstoke, UK). The total amount of propofol (mg) infused during the endoscopy was noted for subsequent analysis.

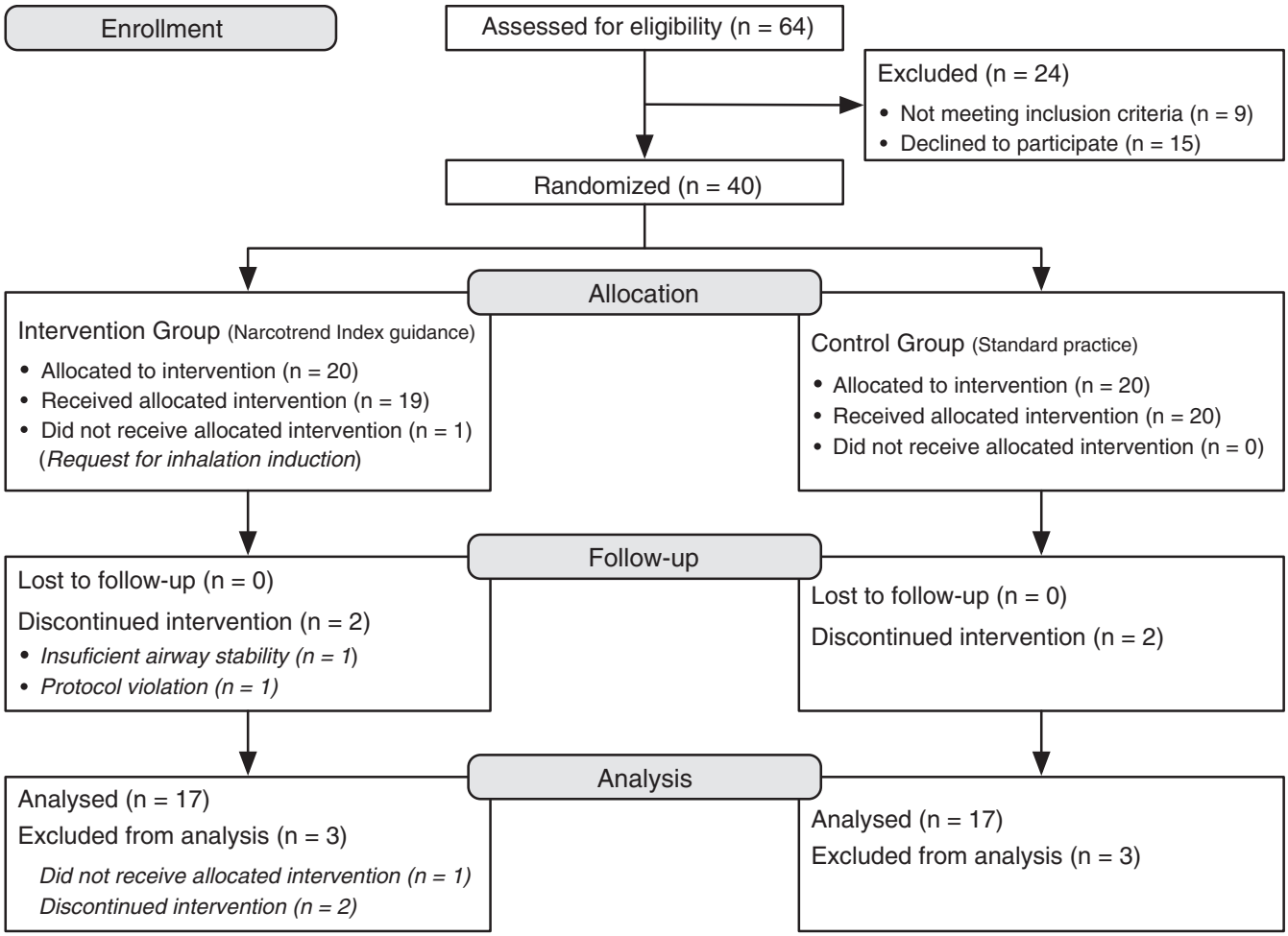

FIGURE 1 Study flow diagram according to the CONSORT 2010 statement

Sedation was initiated using a stepwise increase (1 μg/mL) of propofol every 15 seconds, until either a stable Narcotrend Index of 65 ± 5 (Group NI), or a state of deep sedation, with the patient not being rousable by mild tactile stimulation (Group C), was established. When these milestones were reached, the endoscopy was allowed to be started.

During the endoscopy, in patients randomized to group NI, propofol was titrated in steps of 0.5 μg/mL to maintain a Narcotrend Index of 65 ± 5. We had to take care to keep the likelihood of unintended episodes of intraprocedural awareness with recall as low as possible. Therefore, and due to personal clinical experience of the principle investigator, we aimed at NI values indicating a rather deep level of sedation.[11] We are aware that it is debatable whether our approach should be called deep sedation or light anesthesia with an unsecured airway. The latter definition might confuse readers; therefore, we decided to call our approach procedural sedation and analgesia.

In patients randomized to group C, Narcotrend Index data were unavailable to the pediatric anesthesiologist in charge. Propofol dosing was entirely based on conventional clinical surrogate parameters of depth of hypnosis, such as heart rate, blood pressure, and patient movement. The same 0.5 μg/mL titration steps as in group NI were applied to achieve and maintain good endoscopy conditions.

Remifentanil was infused starting at a continuous rate of 0.025 μg/kg/min, irrespective of study group allocation. In case of clinical signs of discomfort or purposeful movement, remifentanil infusion was increased to 0.05 μg/kg/min, whereas in the event of a respiratory rate of ≤10/min, the infusion rate was lowered to 0.01 μg/kg/min.

Patients were breathing spontaneously throughout the sedation procedure, having oxygen 3 L/min applied via a nasal cannula.

Immediately after removal of the endoscope at the end of the procedure, anesthetic drug infusions were discontinued. An investigator who was blinded to patient group allocation entered the operating room and started to assess the patients' course of recovery from procedural sedation using the "Steward Recovery Score from Anaesthesia".[12] Predefined criteria for discharge from the operating room to the recovery room were responsiveness to stimulation, good airway maintenance, and nonpurposeful movements, equaling to a Steward score of 3 out of 6. The time interval between discontinuation of propofol delivery and reaching a Steward score of 3 was defined as the primary outcome parameter of this trial.

The following secondary outcome parameters were defined: Propofol consumption (mg/kg/h) during the endoscopy, the time interval between the end of the procedure and meeting discharge

criteria from the recovery room (Steward score of 6), the distribution of Narcotrend Index values during the endoscopy (within, below, or above the target range of 65 ± 5), the incidence of recall of events during the endoscopy (assessed by a Brice interview [13] on 3 occasions), the assessment of the endoscopy conditions by the pediatric gastroenterologist (good—acceptable—difficult) and adverse effects. We had also planned an economic analysis (cost minimization analysis). Unfortunately, due to legal restrictions regarding the publication of economic data, which we were not aware of when we designed this study, we were unable to perform that analysis.

2.2 | Randomization

Patients were allocated to the intervention or the control group according to a block-randomization scheme (6-8-8-8-10 = 40), generated by the principle investigator (F.W.) using the website Randomization.com (http://www.randomization.com). F.W. was the anesthesiologist who delivered procedural sedation to all study patients and was therefore not blinded regarding patient allocation to study groups.

2.3 | Power analysis

To detect a difference of 30% less time to meet discharge criteria from the operating room (Steward Score of 3) in the intervention group, with an alpha level of significance fixed at .05 and a beta level of .20, the number of patients required in each study group was 18. This expected difference was based both on previously published data in patients undergoing procedures under general anesthesia [11] or sedation [14] and personal experience of the principle investigator (F.W.) of this study. In order to compensate for possible dropouts due to any kind of protocol violation, a sample size of 2 × 20 study patients was chosen. Sample size was calculated both for both a Student's *t* test (n = 2 × 17 subjects) and a Mann-Whitney *U* test (n = 2 × 18 subjects) using G*Power 3.1.[15]

2.4 | Statistical analysis

Data analysis was performed by all authors using Prism 7 for Mac OS X (Version 7.0C, GraphPad Software Inc., La Jolla, CA, U.S.A.). Continuous data were tested for normality using the D'Agostino and Pearson omnibus normality test. Intergroup comparisons of continuous data were performed using an unpaired *T* test or a Mann-Whitney *U* test. Categorical data were compared by a chi-square or Fisher's exact test. Continuous data are presented as mean(sd) or median [95% CI] as appropriate. *P*-values <.05 were considered significant.

3 | RESULTS

Between May 2014 and October 2015, 40 pediatric patients were recruited. One patient who was already randomized to group NI asked for an inhalation induction and was therefore excluded from participation in the study. Another patient, also allocated to group NI, unexpectedly showed clinical signs of insufficient airway stability after starting procedural sedation. In order to prevent this patient from significant airway obstruction, we decided to switch to general anesthesia with endotracheal intubation, resulting in secondary exclusion. In a third patient randomized to group NI, propofol/remifentanil had to be administered regardless of Narcotrend Index values due to excessive involuntary patient movement during the endoscopy, resulting in secondary exclusion due to protocol violation. Patient and procedural data of the remaining 37 study participants who completed the study are presented in Table 1. Data analysis was performed per protocol.

Regarding the duration of the endoscopic procedures, there was no evidence of a difference between study groups (group NI 20.7 minutes, group C 34.4 minutes); the difference between medians was 13.6 [−6.02 to 19.8] minutes, *P* = .479.

The time interval between the end of the endoscopy (stop propofol delivery) and meeting the criteria for being discharged from the operating room was significantly shorter in group NI than in group C, with a difference between medians of 4.76 minutes [95% CI 2.6 to 7.4 minutes], *P* = .0006. For details see Figure 2.

Propofol consumption during the endoscopic procedure was lower in group NI than in group C, with a difference between medians of 2.1 [95% CI 0.1 to 4] mg/kg/h, *P* = .046.

The time interval from discontinuation of anesthetic drug delivery until discharge criteria from the recovery room were met (Stewart score 6) was shorter in group NI than in group C, with a difference between medians of 4.03 minutes [95% CI 0.81 to 7.61 minutes].

Intergroup comparison of the distribution of Narcotrend Index values (within, above, or below the target range of 65 ± 5) revealed significant intergroup differences on all 3 levels. The percentage of Narcotrend Index values below the target range was lower in group NI than in group C, with a difference between medians of 63% [95% CI 35 to 68%]. Regarding the values within the target range, the percentage in group NI was higher than in group C, with a difference between medians of 37% [95% CI 19 to 41%]. The same accounts for the percentage of values above the target range, with a

TABLE 1 Patient and procedure characteristics

	Group NI	Group C
Age (y)	15.2 (1.6)	15.0 (1.8)
Weight (kg)	53.7 (8.3)	49.0 (8.0)
Gender (female/male)	7/10	11/9
Type of procedure (n)		
EGD	2	5
Ileocolonoscopy	13	9
EGD and Ileocolonoscopy	2	6

Data are presented as mean(sd) or absolute values.
C, control; EGD, esophagogastroduodenoscopy; NI, Narcotrend Index.

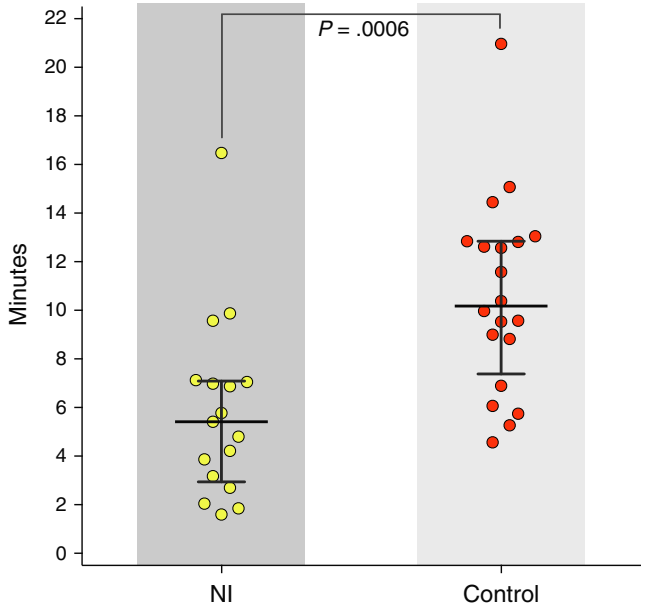

FIGURE 2 Recovery time (discharge readiness from operating room). Individual data (dots) together with median and interquartile range [Colour figure can be viewed at wileyonlinelibrary.com]

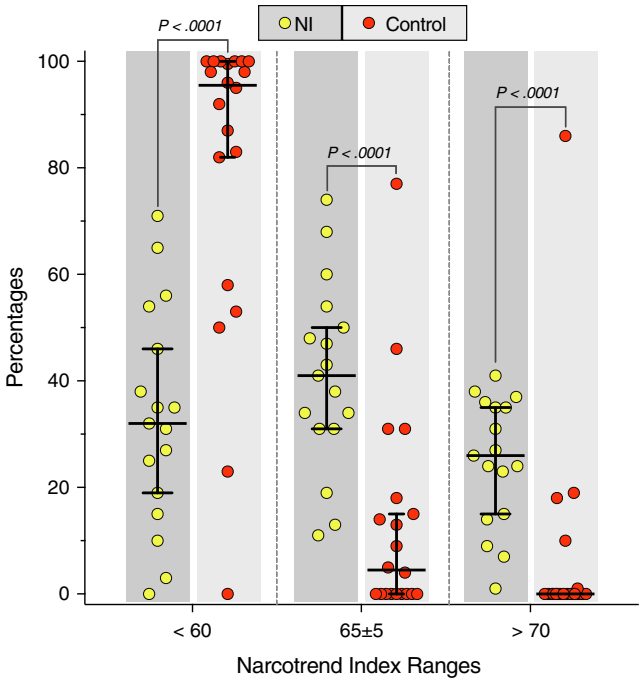

FIGURE 3 Percentage distribution of Narcotrend Index values during endoscopy. Individual data (dots) together with median and interquartile range [Colour figure can be viewed at wileyonlinelibrary.com]

difference between medians of 26% [95% CI 14 to 31]. For more details see Figure 3.

Brice interviews revealed no episodes of awareness with recall during the endoscopy in any patient.

Intergroup comparison of the pediatric gastroenterologists' assessments of endoscopy conditions (good—acceptable—difficult; Group NI: 16-1-0; Group C: 17-3-0) revealed no evidence of a difference. Compared to group C, the relative risk of being assigned to 'acceptable' in group NI was 0.39 [95% CI 0.059 to 2.27], $P = .608$.

There were no episodes of hypoxia in any patient. We observed the following adverse events, all during the induction period, prior to the start of the endoscopy: A jaw-thrust maneuver was required in 1 patient in group NI and 1 patient in group C. Four patients in group C required face mask ventilation, all of them for less than 1 minute.

4 | DISCUSSION

The results of this study, comparing recovery times from procedural sedation and analgesia for pediatric gastrointestinal endoscopy using either EEG-directed propofol delivery or standard practice, provide evidence of the additive value of Narcotrend Index monitoring on the speed of recovery. This applies to meeting discharge criteria from both the operating room (5.4 vs 10.2 minutes) and the recovery room (8.1 vs 11.1 minutes). The accumulated decrease in discharge time from the operating room during an entire endoscopy list could be sufficient to include an additional short procedure.

We used TCI technology for propofol application. Propofol mean effective concentrations (EC_{50}) have been calculated in pediatric patients for a variety of clinical endpoints and scenarios, among them gastrointestinal endoscopy.[8,16] McCormack et al[17] investigated the predictive value of propofol TCI on recovery from anesthesia in children and reported no significant clinical advantage. In our study, we used processed EEG as the leading variable to titrate propofol via TCI. Another advantage of TCI is that during the induction, propofol is injected slower than a usual manual induction bolus, which helps to maintain spontaneous ventilation.[18]

Powers et al[14] used the Bispectral Index (BIS) for titration of propofol during procedural sedation in children. A mean propofol dose of 31.2 mg/kg/h, calculated for the entire sedation period, starting with the induction until completion of the endoscopy, was necessary to achieve and maintain a BIS of 45. The average awakening time, defined as eye opening, was 13.89 minutes. These data are difficult to compare with ours for several reasons: A BIS of 45 is close to the lower end of the range recommended for maintenance of general anesthesia (BIS 40-60) rather than for maintenance of (deep) sedation. Using propofol as the sole agent is furthermore different from our approach, where we used remifentanil and propofol in combination. Like Powers et al, we failed to keep our patients allocated to the intervention group within the Narcotrend Index target range throughout the endoscopy. Narcotrend Index-guided propofol titration resulted in a median[IQR] percentage of 41[31 to 52] of Narcotrend Index values within the target range of 60-70.

In our control group, as revealed by post hoc analysis of Narcotrend Index data, this median percentage was as low as 4.5[0 to 17.3]. The percentages of Narcotrend Index values lower than the target range, representing possible oversedation, were 32[17 to 50]% when using Narcotrend Index guidance, as opposed to 95.5[64

to 100]% in the control group. The opposite was the case when looking at Narcotrend Index values above the target range, representing possible undersedation (group NI: 26[14.5 to 35.5]%; group C: 0[0 to 0.75]%).

Oversedation may be associated with cardiorespiratory compromise, whereas under- sedation can cause intraprocedural awareness with recall. During PSA with an unsecured airway, which, in patients undergoing esophagogastroduodenoscopy is even inaccessible without interrupting the procedure, airway compromise due to hypoventilation is a significant safety issue, as opposed to patients under general anesthesia, having their airway secured by an endotracheal tube or a laryngeal mask. In our study, we did not encounter these adverse events in any of our patients.

4.1 | Patient safety aspects

There is an ongoing debate about safety issues associated with deep sedation for pediatric gastrointestinal endoscopy.[4-6,19-22] This debate is about drug safety, patient selection, care givers' competencies, and institutional issues. What our results add to the drug safety discussion is that Narcotrend Index-guided dosing of propofol, using TCI technology, results in a significant reduction of episodes of undesired oversedation, compared to conventional treatment protocols. Though we strongly recommend our concept of deep sedation for pediatric GE, using Narcotrend-guided propofol delivery, augmented with remifentanil, we shall not forget mentioning that this recommendation is only under the following prerequisites: Patients have to be screened carefully regarding their eligibility for PSA. Caregivers need to be sufficiently skilled in pediatric airway management, including emergency situations. Institutions must be adequately equipped to run a pediatric sedation program, regarding both facilities and skilled personnel. Last but not least, it is our personal impression that delivering PSA in children requires an exceptional high level of situational awareness regarding all aspects of patient safety and comfort. Close communication between the pediatric gastroenterologist and the pediatric anesthesiologist is indispensable.

This study was conducted in pediatric patients aged 12-17 years. There is sufficient evidence from the scientific literature that processed EEG provides us with reliable information regarding the DoH in this patient age group.[23,24] Care must be taken not to extrapolate the results of this study to significantly younger children or even infants. This is both due to the fact that young age is a known risk factor when delivering PSA,[19] and maturational aspects of the EEG, which make DoH monitors less reliable in young children.[23,24]

4.2 | Shortcomings

Using DoH monitoring to titrate hypnotic drugs without feeling uneasy about relying on the information provided by the DoH monitor, needs at least some degree of experience in using that technology. In our study, sedation was given by a single pediatric anesthesiologist (F.W.), with long time experience in using DoH monitoring in children. As already mentioned by Roizen and Toledano,[25] being accustomed to the use of certain technology in a certain group of patients improves outcomes in all patients. There is thus a chance that propofol dosing in the control group was slightly influenced by a "sub-conscious" influence of the experience derived from using DoH monitoring in other patients before. To minimize the chance of learning-contamination bias, patients randomized to group NI should their sedation preferably have been given by an anesthesiologist accustomed to the use of the Narcotrend, whereas the anesthesiologist responsible for patients randomized to group C should have no experience at all in the use of DoH monitoring. Unfortunately, we did not have enough research staff available to perform the study that way.

It would have added significance to the results of our study if we had effect site concentration TCI models available for both propofol and remifentanil. Unfortunately, the plasma concentration Paedfusor model is currently the only TCI algorithm registered for use in pediatric patients in the Netherlands.

5 | CONCLUSIONS

In this prospective randomized controlled study, conducted in pediatric patients aged 12-17 years, Narcotrend Index guidance of propofol sedation for gastrointestinal endoscopy resulted in a significantly faster recovery than standard practice relying on clinical surrogate parameters of hypnotic depth. In this patient age group and clinical setting, NI guidance of procedural sedation can be regarded as safe and effective.

IRB APPROVAL

Medische Ethische Toetsingscommissie Erasmus MC, Rotterdam, The Netherlands, MEC-2013-180; July 11, 2013.

CLINICAL TRIAL NUMBER

Nederlands Trial Register - NTR4593

CONFLICT OF INTEREST

The authors report no conflict of interest.

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How to cite this article: Weber F, Walhout LC, Escher JC. The impact of Narcotrend™ EEG-guided propofol administration on the speed of recovery from pediatric procedural sedation—A randomized controlled trial. *Pediatr Anesth*. 2018;28:443-449. https://doi.org/10.1111/pan.13365