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Moderate-to-Deep Sedation Using Target-Controlled Infusions of Propofol and Remifentanil: Adverse Events and Risk Factors: A Retrospective Cohort Study of 2937 Procedures

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BACKGROUND: In the University Medical Center Groningen in Groningen, the Netherlands, moderate-to-deep sedation is provided by nursing staff trained and supervised by the anesthesia department using protocol-based target-controlled infusions (TCIs) of propofol and remifentanil. The aim of this retrospective cohort study was to investigate the incidence of events with potential adverse health consequences within this service model and the risk factors for the occurrence of these events.

METHODS: We retrospectively interrogated a database containing the computerized anesthetic records of 2937 procedures where moderate-to-deep sedation was provided using TCI administration of propofol and remifentanil between May 2014 and October 2017. The primary outcome measures were the incidence of sedation-related events with potential adverse health consequences and risk factors for the occurrence of such events. The events under investigation were unplanned intensive care unit (ICU) admission, need for cardiopulmonary resuscitation (CPR), death on the day of the procedure due to sedation-related events, cardiovascular events (arrhythmias, hypertension, and hypotension), pulmonary events (aspiration, desaturation, unplanned tracheal intubation), anaphylactic or allergic reactions, and the termination of the procedure due to sedation-related events. Cardiovascular and pulmonary events were classified as severe, significant, or moderate. Events were identified by using computer algorithms to search the computerized records from all included procedures.

RESULTS: Data from 2937 procedures were analyzed. No patients suffered catastrophic events (death, need for CPR, or unplanned ICU admission). Thirty-two severe sedation-related events occurred in 32 procedures. Severe desaturation (0.6%; 95% confidence interval [CI], 0.4–0.9) and severe hypertension (0.2%; 95% CI, 0.04–0.37) were the most common severe events. Significant hypotension (8.8%; 95% CI, 7.73–9.77) and significant desaturation (1.6%; 95% CI, 1.12–2.02) were found to be the most common events with potential adverse health consequences. No patient suffered lasting health consequences. Average mean and maximum targeted effect-site concentrations (Cet) for propofol were 2.6 ± 0.83 and 3.3 ± 1.09 $\mu g \cdot mL^{-1}$, respectively, and for remifentanil 0.84 ± 0.18 and 0.99 ± 0.22 $ng \cdot mL^{-1}$, respectively. Maximum Cets of propofol were lower among patients with higher body mass index (BMI) and were higher among patients of younger age. Higher BMI was a risk factor for desaturation. Increased age and lower BMI were risk factors for hypotension. Longer procedure time was a risk factor for both desaturation and hypotension.

CONCLUSIONS: Moderate-to-deep sedation by propofol and remifentanil TCI has a low incidence of catastrophic and severe events. (Anesth Analg 2020;131:1173–83)

KEY POINTS

- **Question:** What is the incidence of events with potential adverse health consequences during moderate-to-deep sedation provided by nursing staff trained and supervised by the anesthesia department using target-controlled infusions (TCIs) of propofol and remifentanil?
- **Findings:** Moderate-to-deep sedation (MDS) provided by sedation practitioners using TCI propofol and remifentanil under indirect supervision of an anesthesiologist has a low incidence of sedation-related events: 0% and 1.1% for catastrophic events and significant events, respectively.
- **Meaning:** These findings suggest that this service model, where nursing staff trained by the anesthesia department use TCI of propofol and remifentanil to provide MDS under indirect supervision of an anesthesiologist, is associated with an incidence of sedation-related events that is consistent with the results of published studies of other MDS service models.

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Reprints will not be available from the authors.

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GLOSSARY

ASA = American Society of Anesthesiologists; **ASA PS** = American Society of Anesthesiologists physical status; **BMI** = body mass index; **Cet** = targeted effect-site concentration; **CI** = confidence interval; **CONSORT** = CONsolidated Standards Of Reporting Trials; **CPR** = cardiopulmonary resuscitation; **CRNA** = Certified Registered Nurse Anesthetist; **CS-EZIS** = ChipSoft Elektronisch Zorg Informatie Systeem; **EBUS** = endobronchial ultrasound; **ECG** = electrocardiogram; **EP** = (cardiac) electrophysiology; **ERCP** = endoscopic retrograde cholangiopancreatography; **EUS** = esophageal ultrasound; **GI** = gastrointestinal; **ICU** = intensive care unit; **IP** = interventional pulmonology; **IR** = interventional radiology; **MDS** = moderate-to-deep sedation; **NPA** = nasopharyngeal airway; **NVA** = Nederlandse Vereniging voor Anesthesiologie (Dutch Society for Anesthesiology); **OAA/S** = Observer's Assessment of Alertness and Sedation; **PTCD** = percutaneous transhepatic cholangio-drainage; **RFA** = radiofrequency ablation; **SP** = sedation practitioner; **Spo_2** = peripheral oxygen saturation; **SVT** = supraventricular tachycardia; **TCI** = target-controlled infusion; **TEE** = transesophageal echocardiography; **UMCG** = University Medical Center Groningen; **VT** = ventricular tachycardia

Target-controlled infusions (TCIs) of propofol and remifentanil can be used to provide moderate-to-deep sedation (MDS) during diagnostic or therapeutic procedures. Previous studies have explored the optimal targeted effect-site concentrations (Cets) for use during esophagoscopy and colonoscopy.[1–3] In 2012, our department used the findings of these studies to develop a protocol for MDS after new Dutch national guidelines called for increased involvement of anesthesia departments in local MDS service models. The protocol advises titrating Cet-propofol to achieve the desired sedation level, while keeping Cet-remifentanil relatively low and constant. The protocol was developed to be used by sedation practitioners (SPs) during all types of procedures for which patients of American Society of Anesthesiologists physical status (ASA PS) I–IV required MDS.

SPs are nursing staff trained by the anesthesia department and work under the indirect supervision of an anesthesiologist. Between May 2014 and November 2017, this service model was fully operational and the protocol was used to guide MDS provision during >2900 diagnostic or therapeutic procedures in the departments of cardiology, radiology, gastroenterology (GI), and pulmonology.

The primary objective of this study was to evaluate the safety and practice of the use of TCI propofol and remifentanil after the first 3.5 years of experience in our hospital by investigating the occurrence of sedation-related events with potential adverse health consequences and the risk factors associated with the occurrence of these events.

METHODS

Because this is a retrospective observational study, it does not fall under the Dutch Medical Research Involving Human Subjects Act. The institutional review board approved the protocol and waived the need for informed consent (METc-number 2018/106).

The primary outcomes for this study were the incidences of sedation-related events with potential adverse health consequences. The events were classified as catastrophic, severe, significant, or moderate. The definitions of events (Table 1) were based on the official list of recognized anesthetic complications of the Dutch Society for Anesthesiology (Nederlandse Vereniging voor Anesthesiologie [NVA]), existing literature, and the anesthetic targets used in our hospital.[4–6]

Catastrophic Events

- Same-day death: death due to sedation-related events on the day of the procedure;
- Cardiopulmonary resuscitation (CPR): cardiopulmonary arrest requiring Advanced Life Support; and
- Unplanned intensive care unit (ICU) admission: postprocedural ICU admission due to sedation-related events.

Severe Events (Based on NVA List of Anesthesiological Complications)

- Severe hypertension: blood pressure over 220/110 mm Hg, longer than 5 minutes, requiring treatment;
- Severe hypotension: mean arterial pressure below 40 mm Hg, longer than 5 minutes requiring treatment;
- Severe bradycardia: heart rate below 20 bpm for any duration of time;
- Severe tachycardia: heart rate over 200 bpm for any duration of time;
- Unplanned tracheal intubation: tracheal intubation for respiratory insufficiency;
- Severe desaturation: peripheral oxygen saturation (Spo_2) below 85%, longer than 5 minutes requiring treatment;
- Aspiration: aspiration of gastric content evidenced by bronchoscopy; and
- Anaphylaxis: allergic reaction requiring adrenaline and antihistamine.

Significant Events

- Significant hypotension: mean arterial pressure below 65 mm Hg, longer than 10 minutes requiring treatment;

Table 1. Event Definitions and OAA/S Scale

Catastrophic events	
Same-day death	Death due to sedation-related events on the day of the procedure
Cardiopulmonary resuscitation	Cardiopulmonary arrest requiring Advanced Life Support
Unplanned ICU admission	Postprocedural ICU admission due to sedation-related events
Severe events	
Severe hypertension	Blood pressure over 220/110 mm Hg for >5 min, requiring treatment
Severe hypotension	Mean arterial pressure below 40 mm Hg for >5 min requiring treatment
Severe bradycardia	Heart rate below 20 bpm for any duration of time
Severe tachycardia	Heart rate over 200 bpm for any duration of time
Unplanned tracheal intubation	Tracheal intubation for respiratory insufficiency
Severe desaturation	Spo_2 below 85% for >5 min requiring treatment
Aspiration	Aspiration of gastric content evidenced by bronchoscopy
Anaphylaxis	Allergic reaction requiring adrenaline and antihistamine
Significant events	
Significant hypotension	Mean arterial pressure below 65 mm Hg for >10 min requiring treatment
Significant bradycardia	Heart rate below 40 bpm for >5 min requiring atropine
Significant desaturation	Spo_2 below 90% for >5 min requiring treatment
Allergic reaction	Allergic reaction not requiring adrenaline and antihistamine
Moderate events	
Hypotension	Mean arterial pressure below 65 mm Hg for 5–10 min requiring treatment
Bradycardia	Heart rate below 40 bpm not requiring atropine
Desaturation	Spo_2 below 90% for 1–5 min requiring manual airway intervention
Abandoned procedure	Inability to reach adequate sedation depth for procedure
OAA/S scale[7]	
Responds readily to name spoken in normal tone	5
Lethargic response to name spoken in normal tone	4
Responds only after name is called loudly and/or repeatedly	3
Responds only after mild prodding or shaking	2
Does not responds to mild prodding or shaking	1

Abbreviations: ICU, intensive care unit; OAA/S, Observers Assessment of Alertness and Sedation Scale; Spo_2, peripheral oxygen saturation.

- Significant bradycardia: heart rate below 40 bpm, longer than 5 minutes requiring atropine;
- Significant desaturation: Spo_2 below 90% for >5 minutes requiring treatment; and
- Allergic reaction: allergic reaction not requiring adrenaline/antihistamine.

Moderate Events

- Hypotension: mean arterial pressure below 65 mm Hg for 5–10 minutes requiring treatment;
- Bradycardia: heart rate below 40 bpm not requiring atropine;
- Desaturation: Spo_2 below 90% for 1–5 minutes requiring manual airway intervention; and
- Abandoned procedure: inability to safely reach adequate sedation depth for procedure.

Clinical Management

Patients received MDS by SPs working individually under indirect supervision of an anesthesiologist. With this level of supervision, the anesthesiologist was not present in the treatment room but was in the hospital and immediately available for consultation and assistance in case of an emergency. A maximum of 4 SPs was supervised at any moment. The SPs were recruited from the ranks of experienced anesthesia nurses in our hospital. In the Netherlands, anesthesia nurses undergo a 3-year training program. They assist anesthesiologists and, when qualified, are authorized to care for stable patients during the maintenance phase of general anesthesia with indirect supervision. They monitor the patient and initiate minor interventions to adjust the depth of anesthesia and to keep physiological parameters within boundaries set by the anesthesiologist. They are skilled in basic airway maneuvers, the use of vasopressors, and the timely detection of signals of impending emergencies.

Qualified anesthesia nurses who train to become SPs undergo a year of extra training following a national curriculum that expands on their operating theater role. They are trained to screen patients, to administer MDS, and to ensure a safe recovery period, all under indirect supervision of an anesthesiologist. The role and responsibilities of SPs can be compared to that of Certified Registered Nurse Anesthetists (CRNAs) in the United States.

All patients receiving MDS were screened using the standard protocol for preanesthetic screening. Patients with unstable pulmonary, cardiac, or endocrine disease and patients requiring acute (within 1 hour) procedures were not treated using this protocol but received anesthesia care from a team consisting of an anesthesiologist and an anesthesia nurse.

Patient monitoring consisted of continuous 3-lead electrocardiogram (ECG), Spo_2, respiration rate, and end-tidal CO_2. Noninvasive blood pressure

measurements and sedation depth scoring using the Observer's Assessment of Alertness and Sedation scale (OAA/S scale, Table 1)[7] were done every 5 minutes. To facilitate working in locations outside the operating theater, mobile sedation work stations were equipped with a Philips MP30 Anaesthesia monitor (Philips Medizin Systeme Boeblingen GmbH, Boeblingen, Germany), infusion pumps (Alaris plus PK; Becton Dickinson, San Diego, CA), and a computer that automatically stored all data from the monitor and infusion pumps in the electronic medical record system (ChipSoft Elektronisch Zorg Informatie Systeem [CS-EZIS]; ChipSoft BV, Amsterdam, the Netherlands). The workstation also contained all necessary emergency equipment.

The departmental protocol for MDS is based on the study of LaPierre et al[3] and uses propofol (20 $mg \cdot mL^{-1}$) administration by effect-site TCI using the Schnider model[8] and remifentanil (50 $\mu g \cdot mL^{-1}$) administered using the Minto model.[9] The infusions are started simultaneously at Cets of 1.0 $\mu g \cdot mL^{-1}$ (propofol) and 1.0 $ng \cdot mL^{-1}$ (remifentanil). Sedation depth is adjusted primarily by changing the Cet-propofol, in increments or decrements of 0.2–0.5 $\mu g \cdot mL^{-1}$. The Cet-remifentanil is typically left constant during the procedure but can be lowered on indication using decrements of 0.1–0.5 $ng \cdot mL^{-1}$. Cet-remifentanil is only rarely increased. Decisions to adjust the Cet of propofol or remifentanil are made based on the patient's comfort level and the effects of the drugs on cardiopulmonary function, taking into account anticipated painful or unpleasant stages in the procedure.

The targeted depth of sedation was a OAA/S score of 3 to 2. After the procedure, patients remained in a recovery room until the sum of the modified Aldrete score and an additional nausea score (nausea/vomiting = 0 points; nauseous, adequately treated = 1 point; no nausea = 2 points) was 11 or higher. Patients requiring lighter forms of sedation were treated by the proceduralist with other sedatives and opioids without the involvement of the anesthesia department and thus were not included in this study.

We identified all procedures during which patients received MDS between May 1, 2014 (the date of the start of delivery of MDS in the University Medical Center Groningen (UMCG) using the service model described above) to November 1, 2017. Throughout this period, the CS-EZIS system was used to create electronic records for all patients undergoing procedures. After November 1, 2017, CS-EZIS was replaced with a different system and the database was locked.

CS-EZIS automatically records, with 15-second intervals, all physiological data and drug infusion information from all monitors and pumps used during the procedure. In addition, users log clinical findings and interventions in the system using predefined selection item lists. This creates a complete anesthesia record with medicolegal status. The records of these procedures were analyzed using a priori criteria to find evidence of sedation-related events with potential adverse health consequences. To identify events, computer scripts programmed in R (R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org/) were used to search the recorded measurements of the patient's ECG, Spo_2, end-tidal CO_2, pulse rate, respiration rate and blood pressure, and the recordings from the TCI pumps and the user listed interventions. Two authors (C.R.M.B., M.K.D.) independently reviewed the results from these searches and analyzed the anesthetic records of procedures involving catastrophic and severe events, ICU admissions, and deaths within 30 days to rule out artifacts or events not related to sedation. When they did not reach consensus, a third author was involved (A.R.A.) to make a final decision. In addition, catastrophic and severe events were retrieved from the departmental complication register where such events are recorded including the long-term health consequences to the patient to analyze any lasting health consequences.

Statistical Methods

This article adheres to the applicable CONsolidated Standards Of Reporting Trials (CONSORT) guidelines. Statistical analyses were performed with IBM SPSS Statistics, Version 23.0.0.3 (IBM, Armonk, NY). Distributions were visually examined as histograms and tested for normality with the Kolmogorov–Smirnov test. Differences in the incidences of complications between groups were tested with Fisher exact test. Two independent samples *t* test was used to compare normally distributed variables between groups. Mann–Whitney tests and Kruskal–Wallis tests were used for nonparametric variables. Bonferroni-type corrections for multiple pairwise comparisons between groups were applied to the *P* values shown in Tables 2 and 3. *P* values <.05 were considered statistically significant. Risk factors for the occurrence of any degree of hypotension and desaturation (severe, significant, or moderate) were identified using a conditional stepwise backward logistic regression model. Based on existing literature,[5,10–13] ASA PS, age, sex, body mass index (BMI), and procedure duration were candidates as covariates in this model. For each step, variables with *P* values ≥.05 were excluded from the model. In the final model, only covariates with *P* values <.05 remained.

Sample Size and Power Analysis

For the post hoc power analysis of this observational study, we used an online sample size calculator.[14] We defined power = 0.90; expected event rate (for

Table 2. Number of Procedures and Patient Characteristics per Specialty

	TEE	EP	IR	GI	IP	Total
Procedures	77	343	89	1245	1183	2937
Patients (n)	59	312	33	833	1078	2315
ASA PS						
I	0	8	3	70	52	
II	40	263	57	786	638	
III	37	70	28	384	484	
IV	0	2	1	5	9	
Duration of procedures, min	29 ± 10	170 ± 71	81 ± 47	70 ± 34	47 ± 17	
OAA/S score	3 [2–3]	2 [2–3]	2 [2–3]	2 [2–2][a]	2 [2–3]	
Age	58 ± 14	56 ± 15	60 ± 13	54 ± 17	63 ± 12[b]	
BMI	26.7 ± 4.6	26.3 ± 4.3	25.2 ± 5.1	25.0 ± 5.0[c]	25.8 ± 4.9	
% Males	54.5%	57.1%	58.4%	44.9%	58.3%	

Procedure time (minutes) in mean ±SD. Age and BMI are in mean ± SD. All test involved 10 pairwise comparisons.

Abbreviations: ASA PS, American Society of Anesthesiologists physical status; BMI, body mass index; EP, cardiac catheterization; GI, gastroenterology; IP, interventional pulmonology; IR, interventional radiology; OAA/S, Observer's Assessment of Alertness and Sedation; SD, standard deviation; TEE, transesophageal echocardiography.

[a]Lower than all other specialties ($P < .01$).

[b]Sign higher than EP and GI ($P < .01$).

[c]Lower than all others ($P < .01$).

Table 3. Maximum Cet-Propofol (μg·mL^{-1}) and Cet-Remifentanil (ng·mL^{-1})

	Cet-Propofol Mean ± SD (IQR)	Cet-Remifentanil Mean ± SD (IQR)
Specialty		
TEE	3.3 ± 0.9 (2.7–4)	0.9 ± 0.1 (0.8–1)
EP	2.2 ± 0.8[a] (1.6–2.7)	0.8 ± 0.2[b] (0.7–1)
IR	3.1 ± 1.3 (2.2–3.7)	1.0 ± 0.2 (0.9–1)
IP	3.3 ± 1.1 (2.6–4)	0.9 ± 0.2 (1–1)
GI	3.9 ± 2.1[c] (3–4.4)	1.0 ± 0.2[d] (1–1)
ASA PS		
I	3.8 ± 1.0 (3–4.5)	1.0 ± 0.1 (1–1)
II	3.5 ± 1.7[e] (2.8–4)	0.9 ± 0.2 (1–1)
III	3.2 ± 1.6[e] (2.5–3.8)	0.9 ± 0.2[f] (1–1)
IV	2.5 ± 0.8[e] (2–3)	1.0 ± 0.3 (0.9–1)
Age groups		
18–40	3.9 ± 1.2 (3.2–4.5)	1.05 ± 0.2 (1–1)
41–65	3.5 ± 1.4[g] (2.8–4)	1.00 ± 0.2[h] (1–1)
66–80	3.1 ± 1.0[g] (2.5–3.7)	0.94 ± 0.2[i] (0.9–1)
Over 80	2.7 ± 0.5[g] (2.45–3)	0.92 ± 0.1[i] (0.8–1)
BMI class (kg·m^{-2})		
1 (<20)	3.4 ± 1.1 (2.7–4)	0.9 ± 0.2 (1–1)
2 (20–<25)	3.5 ± 1.1[j] (2.8–4)	0.9 ± 0.1 (1–1)
3 (25–<30)	3.3 ± 1.0 (2.5–4)	0.9 ± 0.1 (1–1)
4 (30–<35)	3.5 ± 1.0 (2.5–3.8)	0.9 ± 0.3 (1–1)
5 (35–<40)	3.1 ± 1.0 (2.5–3.7)	1.0 ± 0.1 (0.9–1)
6 (≥40)	3.0 ± 1.0 (2.4–3.6)	0.9 ± 0.1 (1–1)

Abbreviations: ASA PS, American Society of Anesthesiologists physical status; BMI, body mass index; Cet, targeted effect-site concentrations; EP, cardiac catheterization; GI, gastroenterology; IP, interventional pulmonology; IQR, interquartile range; IR, interventional radiology; SD, standard deviation; TEE, transesophageal echocardiography.

[a]Lower than all other specialties ($P < .01$;10 pairwise comparisons).

[b]Lower than IP, IR, GI.

[c]Higher than all other specialties($P < .01$; 10 pairwise comparisons).

[d]Higher than IP and TEE ($P < .01$; 10 pairwise comparisons).

[e]Maximum Cet-propofol different between all ASA PS ($P < .01$; 6 pairwise comparisons), except ASA PS III–IV ($P = .152$; 6 pairwise comparisons).

[f]Lower than ASA PS I ($P = .032$; 6 pairwise comparisons) and ASA PS II ($P < .01$; 6 pairwise comparisons).

[g]Cet-propofol maximum difference between all age groups ($P < .01$; 6 pairwise comparisons).

[h]Higher than age group 1 ($P = .023$; 6 pairwise comparisons).

[i]Lower than age groups 3, 2, and 1.

[j]Significantly higher than classes 3–4 and 5 ($P < .01$; 15 pairwise comparisons).

cardiopulmonary arrest) = 0.094%, based on previous literature[5]; and critical tolerance limit = 1 event. The calculated sample size was 2450. Given that the sample size of our study (2937) exceeds, this value we conclude that the post hoc power of our study exceeds 0.9.

RESULTS

In total, the data of 2937 procedures performed in 2315 adult patients under MDS were analyzed. MDS was provided for the specialties cardiology (transesophageal echocardiography [TEE] and cardiac electrophysiology [EP; ablation for (supra-)ventricular tachycardia]), interventional radiology (IR; percutaneous transhepatic cholangio-drainage [PTCD] and radiofrequency ablation), GI (upper/lower endoscopy, endoscopic retrograde cholangiopancreatography), and interventional pulmonology (IP; esophageal/endobronchial ultrasound). Patient and procedure characteristics are presented in Table 2. Patients of ASA PS I to IV were treated. Of the patients, 52.2% were men, and 47.8% were women. The majority (65.3%) of patients were classified as ASA PS II–III. All procedures were elective or urgent (needing treatment within 24 hours). Mean age was 57.9 ± 15.0. Mean age of patients undergoing pulmonary procedures was higher ($P < .01$) than the age of cardiac or GI patients. Mean BMI was 25.5 ± 4.8; 16.6% of the patients were obese (BMI >30 kg·m^{-2}). The highest BMI of a patient was 48.2 kg·m^{-2}. This patient's procedure was uneventful. The BMI of patients undergoing GI procedures was significantly lower ($P < .01$) than of those for other specialties.

TCI Administration

Mean Cet-propofol was 2.6 ± 0.83 μg·mL^{-1}, and mean Cet-remifentanil was 0.84 ± 0.18 ng·mL^{-1}. The means of

the maximum Cet-propofol and Cet-remifentanil used during treatments were 3.3 ± 1.09 μg·mL^{-1} and 0.99 ± 0.22 ng·mL^{-1}, respectively (Figure, panels A, B). Cet-propofol and Cet-remifentanil were titrated to achieve the required sedation depth or in response to physiological changes during 2905 and 2721 procedures, respectively. The majority of changes to Cet-remifentanil were decreases in Cet. Maximum targeted sedation depth was OAA/S 3–2 and was reached for 29.5% and 64.7% of patients, respectively. Excessive sedation (OAA/S = 1) occurred in 0.4% of procedures. One of these patients experienced a significant event: significant hypotension. In 5.4%, lighter sedation was sufficient to perform the procedure.

The means of the maximum Cet-propofol and Cet-remifentanil were significantly lower ($P < .01$) in older age groups. Cet-propofol was lower in patients of higher ASA PS ($P < .01$). Table 3 shows the maximum Cet-propofol and Cet-remifentanil grouped by specialty, ASA PS, age, and BMI classes. Patients experiencing any form of desaturation or hypotension (severe, significant, or moderate) had not been administered a higher Cet-propofol compared to patients not suffering from desaturation or hypotension ($P = .782$ and $P = .056$, respectively). Maximum Cet-remifentanil was not different between patients experiencing any form of hypotension (severe, significant, or moderate) and those not experiencing hypotension ($P = .4$). Patients suffering moderate desaturation had significantly lower maximum Cet-remifentanil compared to those who did not (0.94 ± 0.15 vs 0.99 ± 0.22 ng·mL^{-1}; $P = .037$). For severe or significant desaturations, no significant difference was found ($P = .05$ and $P = .54$, respectively).

Catastrophic Events

No same-day deaths occurred. No patient suffered cardiopulmonary arrest or required ICU admission due to sedation-related events (Table 4). One patient (0.03%) was admitted to an ICU 1 day after the procedure with septic shock due to a bowel perforation. Forty-five patients (1.45%) died within 30 days after their procedure. The cause of death was related most often to advanced oncological disease. After review of each of the records, none of these patients' deaths could be related to sedation events and none of these patients had suffered any catastrophic or severe sedation-related event.

Severe Events

Severe events occurred during 32 procedures (32 patients; 1.09%) (Table 4). Six patients (0.2%) suffered an episode of severe hypertension, but none required antihypertensive medication: all episodes were treated by adjusting the sedation depth. Severe hypotension (n = 6, 0.2%) was treated by sedation depth adjustment and ephedrine and phenylephrine. One patient (0.03%) had sinus tachycardia for several seconds that resolved without treatment, 1 (0.03%) patient had a self-limiting severe tachycardia arising from a preexisting atrial flutter, and a third patient developed atrial fibrillation which later converted to sinus rhythm. Of the cases of severe desaturation (n = 19; 0.65%), 6 (0.2%) required bag-mask ventilation. The other patients were treated by adjusting the sedation depth alone (n = 9; 0.31%) or in combination with manual airway maneuvers (n = 4; 0.14%) or a nasopharyngeal airway (NPA) (n = 7; 0.24%). Four procedures (0.14%) were abandoned because of severe desaturations not responding to other treatment. These patients recovered uneventfully. The 3 patients (0.1%) who experienced severe hypotension were treated by adjustment of sedation depth and administration of ephedrine and/or phenylephrine.

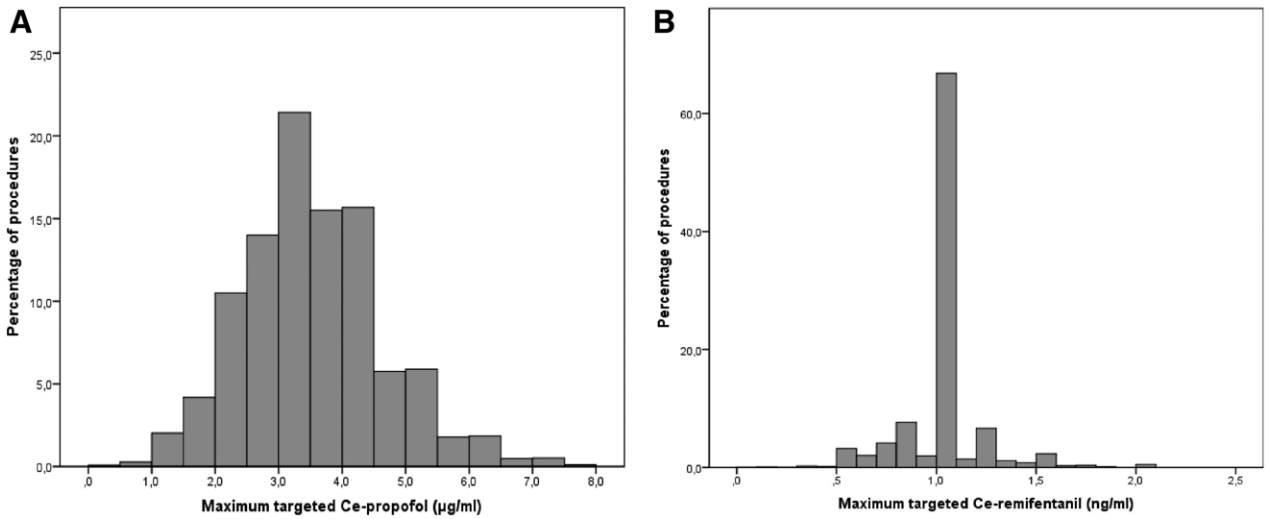

Figure. Targeted effect-site concentrations. A, Frequency of maximum targeted effect-site concentration (propofol). B, Frequency of maximum targeted effect-site concentration (remifentanil).

Table 4. Event Frequencies per ASA PS (n [%])

ASA PS		1	2	3	4
n		133	1784	1003	17
Catastrophic events					
Same-day death	0				
Cardiopulmonary resuscitation	0				
Unplanned ICU admission	0				
Total (catastrophic events)	0				
Severe events					
Severe hypertension	6		5 (0.28)	1 (0.10)	
Severe hypotension	3		2 (0.11)	1 (0.10)	
Severe bradycardia	0				
Severe tachycardia	3		2 (0.11)	1 (0.10)	
Unplanned tracheal intubation	0				
Severe desaturation	19		8 (0.45)	10 (1.00)	1 (5.88)
Aspiration	1			1 (0.10)	
Anaphylaxis	0				
Total (severe events)	32				
Significant events					
Significant hypotension	257	8 (6.02)	159 (8.91)	89 (8.87)	1 (5.88)
Significant bradycardia	0				
Significant desaturation	46		31 (1.74)	15 (1.50)	
Allergic reaction	6		3 (0.17)	3 (0.30)	
Total (significant events)	309				
Moderate events					
Hypotension	64	49 (36.84)	37 (2.07)	24 (2.39)	
Bradycardia	8		5 (0.28)	3 (0.30)	
Desaturation	100	49 (36.84)	63 (3.53)	30 (2.99)	
Abandoned procedure	4		2 (0.11)	2 (0.20)	
Total (moderate events)	176				

Abbreviations: ASA PS, American Society of Anesthesiologists physical status; ICU, intensive care unit.

Aspiration (n = 1; 0.03%) was treated conservatively on the ward. According to the departmental complication follow-up register, no patients suffered lasting health consequences from any of these events.

Significant Events

Significant hypotension was the most common significant event, with the highest frequency during gastroenterological endomucosal resections and ventricular tachycardia (VT) ablations (Table 5). Significant desaturations (n = 46; 1.57%) were managed by adjustment of sedation depth and/or manual airway maneuvers (n = 13; 0.44%) and/or placement of an NPA (n = 31; 1.06%). No bag-mask ventilation was required. Antihistamine administration was sufficient to treat all 6 cases (0.20%) of allergic reactions. The timing of antihistamine administration suggests that neither propofol nor remifentanil can be implicated and the reactions occurred shortly after administration of iodinated contrast.

Moderate Events

Moderate hypotension (n = 64; 2.18%) was treated by adjusting the sedation depth and administration of vasopressors in 49 (1.67%) procedures. In 15 (0.51%) cases, only vasopressors were given and sedation depth was maintained. Moderate desaturation (n = 100; 3.40%) was treated with manual airway maneuvers (n = 100; 3.40%) combined in 49 (1.67%) cases with adjustment of the sedation depth. In 5 occurrences (0.17%), bag-mask ventilation was started early, and in 3 (0.10%) cases, an NPA was placed.

The frequencies of severe, significant, or moderate events between patient groups of different ASA PS did not differ significantly (P = .114; .397; .741, respectively) (Table 4). There was no significant difference in the frequencies of severe, significant, or moderate events across all specialties (P = .58; .06; .4, respectively) (Table 5). Chin lift/jaw thrust (n = 229; 7.8%) and/or placement of an NPA (n = 327; 11.1%) was performed during 425 (14.5%) procedures to prevent or treat respiratory insufficiency. Vasopressors (ephedrine and/or phenylephrine) were administered during 318 (10.8%) procedures.

One hundred fifty-three (5.21%) moderate desaturation events were treated by adjustment of the sedation depth alone, preventing progression to more significant desaturations. Moderate hypotension was treated by adjusting Cet-remifentanil or Cet-propofol during 209 (7.12%) procedures preventing progression to significant hypotension and the need for vasopressors.

Risk Factors for Desaturation and Hypotension

ASA PS, age, sex, BMI, and procedure duration were included as covariates in the initial model used to identify variables associated with desaturation. In the final model, only higher BMI and longer procedure

Table 5. Frequencies of Sedation-Related Events (n [%]) per Procedure Group

		TEE	EP: SVT-Ablation	EP: VT-Ablation	IR: PTCD	IR: RFA	IR: Other Radiology	GI: Upper Endoscopy	GI: Lower Endoscopy	GI: ERCP	Combined GI	IP: EBUS	IP: EUS	IP: Other Bronchoscopy
Catastrophic events	n (%) [95% CI]	(n = 77)	(n = 289)	(n = 54)	(n = 48)	(n = 32)	(n = 9)	(n = 339)	(n = 286)	(n = 492)	(n = 128)	(n = 583)	(n = 256)	(n = 344)
Same-day death	0 (0)													
Cardiopulmonary resuscitation	0 (0)													
Unplanned ICU admission	0 (0)													
Total	0 (0)													
Severe events														
Severe hypertension	6 (0.2) [0.04–0.37]		1 (0.3)					2 (0.6)		2 (0.4)	1 (0.8)			
Severe hypotension	3 (0.1) [0–0.22]		1 (0.3)										2 (0.8)	
Severe bradycardia	0 (0)													
Severe tachycardia	3 (0.1) [0–0.22]									2 (0.4)			1 (0.4)	
Unplanned tracheal intubation	0 (0)													
Severe desaturation	19 (0.6) [0.4–0.9]	1 (1.3)	1 (0.3)					2 (0.6)		3 (0.6)	1 (0.8)	7 (1.2)		4 (1.2)
Aspiration	1 (0) [0–0.1]	1 (1.3)												
Anaphylaxis	0 (0)													
Total	32 (1.1)													
Significant events														
Significant hypotension	257 (8.8) [7.73–9.77]	3 (3.9)	27 (9.3)	11 (20.4)	2 (4.2)	2 (6.3)	1 (11.1)	35 (10.3)	37 (12.9)	23 (4.7)	40 (31.3)	37 (6.3)	38 (14.8)	1 (0.3)
Symptomatic bradycardia	0 (0)													
Significant desaturation	46 (1.6) [1.12–2.02]		7 (2.4)					1 (0.3)		7 (1.4)	3 (2.3)	22 (3.8)	1 (0.4)	5 (1.5)
Allergic reaction	6 (0.2) [0.04–0.37]		1 (0.3)	1 (1.9)					1 (0.3)	2 (0.4)			1 (0.4)	
Total	309 (10.5)													
Moderate events														
Hypotension	64 (2.2) [1.65–2.71]	1 (1.3)	2 (0.7)	2 (3.7)	2 (4.2)	4 (12.5)		8 (2.4)	8 (2.8)	5 (1)	8 (6.3)	16 (2.7)	4 (1.6)	4 (1.2)
Bradycardia	8 (0.3) [0.08–0.46]		2 (0.7)	1 (1.9)		1 (3.1)		1 (0.3)	1 (0.3)	1 (0.2)		1 (0.2)		
Desaturation	100 (3.4) [2.75–4.06]	2 (2.6)	19 (6.6)	2 (3.7)	1 (2.1)		1 (11.1)	5 (1.5)	7 (2.4)	9 (1.8)	4 (3.1)	25 (4.3)	6 (2.3)	19 (5.5)
Abandoned procedure	4 (0.1) [0–0.27]							1 (0.3)		1 (0.2)		1 (0.2)		1 (0.3)
Total	176 (6)													

Abbreviations: CI, confidence interval; EBUS, endobronchial ultrasound and biopsies; EP, electrophysiology; ERCP, endoscopic retrograde cholangiopancreatography; EUS, esophageal ultrasound and biopsies; GI, gastroenterology; ICU, intensive care unit; IP, interventional pulmonology; PTCD, percutaneous transhepatic cholangio-drainage; RFA, radiofrequency ablation; IR, interventional radiology; SVT, supraventricular tachycardia; TEE, transesophageal echocardiography; VT, ventricular tachycardia.

duration remained as significant factors (odds ratio: 1.06; 95% confidence interval [CI], 1.03–1.09; $P < .001$ and odds ratio: 1.30; 95% CI, 1.12–1.51; $P = .01$, respectively). ASA PS, age, sex, BMI, and procedure duration were included as covariates in the initial model used to identify variables associated with the occurrence of hypotension. In the final model, procedure duration (odds ratio: 1.49; 95% CI, 1.33–1.67; $P < .001$), age (odds ratio: 1.04; 95% CI, 1.03–1.05; $P < .001$), and BMI (odds ratio: 0.96; 95% CI, 0.94–0.99; $P = .006$) remained as significant covariates for the occurrence of hypotension.

DISCUSSION

Within the study period, 2937 procedures in our hospital were performed under MDS using TCI propofol and remifentanil. No catastrophic events occurred during these procedures, no patients required unplanned tracheal intubation, the frequency of severe events (1.09%) was low, and no patients suffered lasting health consequences.

TCI was used for all procedures, using the departmental MDS protocol. Our protocol for combining TCI propofol and remifentanil was based on previous studies[1,3] and incorporated in our service model to allow SPs to administer MDS under indirect supervision. Overall, the protocol was closely followed: Cet-propofol was adjusted to control sedation depth, and Cet-remifentanil was kept low and was changed only marginally. Using a higher propofol–lower remifentanil concentration combination is more likely to block the response to esophageal instrumentation while avoiding intolerable ventilatory depression. Using higher remifentanil concentrations combined with lower propofol concentrations increases the chance of intolerable ventilatory depression.[3] Patients who experienced a moderate desaturation tended to have received a lower maximum Cet-remifentanil. We believe this was the result of appropriate prudence of the SPs when confronted with more vulnerable patients. Administration of naloxone was never required.

TCI allows those trained in its use to exercise precise control of the level of sedation.[1,15] The rapid onset and offset of propofol and remifentanil allows for quick adjustments of sedation depth as an intervention.[16] The effects of propofol and remifentanil on circulation and respiration are synergistic,[3,17,18] and, although the maximum targeted sedation depth of OAA/S 3–2 was attained in the vast majority of patients, we also found desaturation and hypotension to be the most common events. The SPs frequently used airway interventions and vasoactive support. The ability to perform these interventions is a basic requirement for safe provision of sedation and anesthesia care, and we consider the acquisition and maintenance of these skills as an essential part of this service model. TCIs will not discharge the responsibility of those providing MDS to remain vigilant and carefully titrate drug administration to balance the patients' safety and comfort.

Patient age, procedure duration, and BMI were independent risk factors for desaturation or hypotension. Although these factors contributed to the risk to a limited extent, these findings are consistent with existing literature. Leslie et al[5] found that a higher BMI increased the risk of significant unplanned intraoperative adverse events, and McVay et al[11] found that patients with a higher BMI experienced more episodes of desaturation and needed chin-lift maneuvers more often. Advancing age increases the patients' sensitivity to anesthetic drugs and reduces their cardiopulmonary physiological reserves,[12,13,19] and long procedures are not only often more complex, but they also expose patients to a longer time at risk of adverse events.

We are as yet unable to explain the negative association of higher BMI with the incidence of hypotensive events, except possibly by the finding that higher maximum Cet-propofol values were used for patients with a normal BMI (Table 3). Possibly this is the result of the fact that the models were not developed from data from obese patients and may not accurately specify the parameters in the obese.[20] The behavior of the model in the obese patient is complex, however, and the current results do not allow for more detailed conclusions.

Our study has some noteworthy strengths and limitations. We acquired the data for this study from automatically stored information of vital signs monitors and we analyzed the data with computer algorithms. This limits observer and recall bias that can accompany studies of clinical practice. For hypotensive events, we have not used relative changes from baseline measurements because these rely on accurate, predefined baseline measurements. We believe this is not feasible and reliable in the practical, clinical setting of MDS. Our blood pressure limits are based on a recent study that showed how anesthetic management of blood pressure can be based on intraoperative pressures without regard to preoperative pressure.[6] We incorporated the need for a skilled intervention in most of the event definitions because, during some procedures, certain changes in physiological measurements are considered acceptable by the specialist performing the procedure (eg, desaturations accepted by the pulmonologist during bronchoscopy and foreseen hemodynamic consequences of catheter ablation of cardiac arrhythmias). Although this opens up the possibility of bias in the reporting of interventions such as vasopressor use or manual airway maneuvers, the chronological connection between vital sign readings

and interventions was established using computer algorithms locating adjustments in Cet-propofol and Cet-remifentanil automatically recorded in our data system. Finally, the caregivers were unaware of this study at the time of the procedures (thus, limiting the Hawthorne effect[21]) and have a vested interest in accurate reporting because the data file of each procedure serves as a legal document of the conduct of the anesthesia care.

One limitation of the current study is that, although it demonstrates a low incidence of catastrophic complications in the cohort studied, it cannot be viewed as a definitive demonstration of the safety of the practice. A second limitation is that we did not collect data on proceduralist satisfaction. However, only 4 procedures were aborted because of an inability to reach an adequate sedation safely, and at regular meetings with the proceduralists, they have consistently expressed their satisfaction with the service model. The study does not have a comparator group: since the introduction of the service model, MDS has been almost exclusively provided by the SPs, while light sedation is performed by proceduralists for healthier patients and different procedure groups. Some comparisons with previous studies can be made, but these studies have used different definitions of events and any comparisons should be made with caution. Catastrophic events did not occur. The frequencies of significant hypotensive and hypoxemic events (8.8% and 1.6%, respectively) are comparable or lower than those reported in other studies of MDS practices.[5,10] The cumulative incidence of catastrophic and severe events found in the current study was also comparable to the incidences of relevant complications of anesthetics care published by our department in a previous study using the same criteria (1.1%; 95% CI, 0.7–1.5 vs 0.9%; 95% CI, 0.8–0.9).[4]

Before the start of this service model, our anesthesiology department was seldom involved in procedural sedation outside the operating theater. Most such procedures were performed under light sedation by the specialists who simultaneously performed the procedure. The new Dutch MDS guidelines required the presence of a professional solely responsible for the sedation during the procedure. In common with many anesthesiology departments in the Netherlands and elsewhere, our department lacked sufficient numbers of anesthesiologists to perform this task. Looking at the results of the current study, we believe that this new service model, involving SPs using TCI propofol and remifentanil under indirect supervision, has safely filled this manpower gap and enabled our hospital to comply with the 2012 guidelines. As of August 2019, the SPs have administered MDS using TCI propofol and remifentanil during almost 5000 procedures. In conclusion, MDS using TCIs of propofol and remifentanil is associated with an incidence of sedation-related events that compares favorably with the results of published literature from other MDS service models. The results of this study suggest that protocol-driven sedation provided by well-trained and equipped SPs, using TCIs of propofol and remifentanil under indirect supervision of an anesthesiologist, is an acceptably safe and successful method of MDS for a broad range of patients and procedures. ■

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Name: Clemens R. M. Barends, MD.
Contribution: This author helped with conception and design of the work; the acquisition, analysis, and interpretation of data for the work; drafting the work; and final approval of the version to be published.
Conflicts of Interest: C. R. M. Barends is a member of Anthony R. Absalom's research group. He has no personal involvement that might raise the question of bias in the work reported or in the conclusions, implications, or opinions stated. His research group/department received (over the last 3 years) research grants and consultancy fees from The Medicines Company (Parsippany, NJ), Masimo (Irvine, CA), Fresenius (Bad Homburg, Germany), Dräger (Lübeck, Germany), Paion (Aachen, Germany), and Medtronic (Dublin, Ireland).
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REFERENCES

1. Moerman AT, Herregods LL, De Vos MM, Mortier EP, Struys MM. Manual versus target-controlled infusion remifentanil administration in spontaneously breathing patients. *Anesth Analg.* 2009;108:828–834.
2. Borrat X, Valencia JF, Magrans R, et al. Sedation-analgesia with propofol and remifentanil: concentrations required to avoid gag reflex in upper gastrointestinal endoscopy. *Anesth Analg.* 2015;121:90–96.
3. LaPierre CD, Johnson KB, Randall BR, White JL, Egan TD. An exploration of remifentanil-propofol combinations that lead to a loss of response to esophageal instrumentation, a loss of responsiveness, and/or onset of intolerable ventilatory depression. *Anesth Analg.* 2011;113:490–499.
4. Westerkamp AC, de Geus AF, Molenbuur B, et al. Comparing peri-operative complications of paediatric and adult anaesthesia: a retrospective cohort study of 81267 cases. *Eur J Anaesthesiol.* 2018;35:280–288.
5. Leslie K, Allen ML, Hessian EC, et al. Safety of sedation for gastrointestinal endoscopy in a group of university-affiliated hospitals: a prospective cohort study. *Br J Anaesth.* 2017;118:90–99.
6. Salmasi V, Maheshwari K, Yang D, et al. Relationship between intraoperative hypotension, defined by either reduction from baseline or absolute thresholds, and acute kidney and myocardial injury after noncardiac surgery: a retrospective cohort analysis. *Anesthesiology.* 2017;126:47–65.
7. Chernik DA, Gillings D, Laine H, et al. Validity and reliability of the Observer's Assessment of Alertness/Sedation Scale: study with intravenous midazolam. *J Clin Psychopharmacol.* 1990;10:244–251.
8. Schnider TW, Minto CF, Shafer SL, et al. The influence of age on propofol pharmacodynamics. *Anesthesiology.* 1999;90:1502–1516.
9. Minto CF, Schnider TW, Egan TD, et al. Influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentanil. I. Model development. *Anesthesiology.* 1997;86:10–23.
10. Koers L, Eberl S, Cappon A, et al. Safety of moderate-to-deep sedation performed by sedation practitioners: a national prospective observational study. *Eur J Anaesthesiol.* 2018;35:659–666.
11. McVay T, Fang JC, Taylor L, et al. Safety Analysis of bariatric patients undergoing outpatient upper endoscopy with non-anesthesia administered propofol sedation. *Obes Surg.* 2017;27:1501–1507.
12. Dundee JW, Robinson FP, McCollum JS, Patterson CC. Sensitivity to propofol in the elderly. *Anaesthesia.* 1986;41:482–485.
13. Khoi CS, Wong JJ, Wang HC, Lu CW, Lin TY. Age correlates with hypotension during propofol-based anesthesia for endoscopic retrograde cholangiopancreatography. *Acta Anaesthesiol Taiwan.* 2015;53:131–134.
14. StatsToDo. Sample Size for Rare Events Program. Available at: https://www.statstodo.com/SSizRareEvent_Pgm.php. Accessed August 29, 2019
15. Absalom AR, Glen JI, Zwart GJ, Schnider TW, Struys MM. Target-controlled infusion: a mature technology. *Anesth Analg.* 2016;122:70–78.
16. Anderson KJ. *Total Intravenous Anesthesia and Target controlled Infusions*. In: Absalom AR, Mason KP, eds. 1st ed. Cham, Switzerland: Springer International Publishing AG; 2017:369.
17. Mertens MJ, Olofsen E, Engbers FH, Burm AG, Bovill JG, Vuyk J. Propofol reduces perioperative remifentanil requirements in a synergistic manner: response surface modeling of perioperative remifentanil-propofol interactions. *Anesthesiology.* 2003;99:347–359.
18. Moerman AT, Struys MM, Vereecke HE, Herregods LL, De Vos MM, Mortier EP. Remifentanil used to supplement propofol does not improve quality of sedation during spontaneous respiration. *J Clin Anesth.* 2004;16:237–243.
19. Mangoni AA, Jackson SH. Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications. *Br J Clin Pharmacol.* 2004;57:6–14.
20. Absalom AR, Mani V, De Smet T, Struys MM. Pharmacokinetic models for propofol–defining and illuminating the devil in the detail. *Br J Anaesth.* 2009;103:26–37.
21. Sedgwick P, Greenwood N. Understanding the Hawthorne effect. *BMJ.* 2015;351:h4672.