

Manual Versus Target-Controlled Infusion Remifentanyl Administration in Spontaneously Breathing Patients

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BACKGROUND: The combination of propofol-remifentanyl for procedural deep sedation in spontaneously breathing patients is characterized by the frequent incidence of side effects, especially respiratory depression. These side effects may be due to either the drug combination or the drug delivery technique. Target-controlled infusion (TCI) might optimize drug delivery. In this prospective, randomized, double-blind study in patients undergoing elective colonoscopy, we thus tried to answer two questions: first, if adding remifentanyl to propofol surpasses the disadvantages of the combination of these two products, and second, if administration of remifentanyl via TCI decreases the incidence of side effects, compared to manually controlled administration.

METHODS: Patients undergoing elective colonoscopy were randomly assigned to receive remifentanyl via manually controlled continuous infusion (MCI) ($0.125 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for 2 min followed by a continuous infusion of $0.05 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$), TCI remifentanyl (1 ng/mL), or placebo (normal saline either as TCI or manual infusion of equivalent rate). All patients received TCI propofol, adjusted to a target concentration level that provided deep sedation in which patients were not responsive to verbal commands, but maintained spontaneous ventilation without assistance.

RESULTS: Significantly more patients in the placebo group showed movement, cough and hiccup, which transiently interfered with the examination. There were no clinically significant differences in hemodynamic or recovery variables among all groups. Remifentanyl administered via TCI resulted in a decrease in propofol requirements. The incidence of hypopnea and apnea was less frequent when remifentanyl was administered via TCI compared to MCI (TCI $n = 7$, MCI $n = 16$, $P < 0.05$).

CONCLUSION: The combination of remifentanyl and propofol for deep sedation in spontaneously breathing patients, offered better conditions for colonoscopy than propofol used as a single drug. Remifentanyl administered via TCI resulted in a decrease in propofol dosing and in a lower incidence in apnea and respiratory depression (TCI $n = 7$, MCI $n = 16$, $P < 0.05$), compared to manually controlled administration of remifentanyl.

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For deep sedation in spontaneously breathing patients, the combination of propofol and remifentanyl is increasing in popularity. However, the ability to provide adequate amnesia, immobility and analgesia is limited by the ventilatory depression associated with both propofol and remifentanyl.¹⁻⁴ The combination of

both products, even in low doses, results in a strikingly synergistic respiratory depression.⁵ In previous work, we compared manually controlled infusion (MCI) of remifentanyl versus placebo to supplement MCI propofol during spontaneous respiration.¹ We concluded that, due to the enormous interindividual variability in calculated effect-site concentrations, MCI remifentanyl in combination with MCI propofol is not a reliable technique during spontaneous respiration.

The administration of drugs via target-controlled infusion (TCI) allows achievement of a defined target concentration without overshoot and overdosing,⁶ which is common when using manual infusions¹ and which is responsible for the respiratory side effects.⁷ TCI versus MCI of remifentanyl used to supplement propofol during spontaneous respiration has not been compared. The aim of this study was twofold. First, to examine if the addition of remifentanyl to propofol TCI would result in more beneficial conditions during procedural deep sedation, and second, if there was a

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further benefit if remifentanyl was administered via TCI compared to manual administration. Therefore, we evaluated the effect of these regimens with regards to (a) calculated propofol and remifentanyl plasma and effect-site concentrations, (b) hemodynamic and recovery variables, and (c) adverse events, with a special focus on respiratory side effects. We hypothesized that remifentanyl administration via TCI would exhibit fewer respiratory effects, and thus contribute to a safer and more reliable technique for coadministration of propofol and remifentanyl in spontaneously breathing patients.

We want to emphasize that patients undergoing colonoscopy were only chosen as a study population. The reader must be cautioned that this article is not at all meant to make any clinical recommendations concerning deep sedation for colonoscopy.

METHODS

After local Ethics' Committee (Ethics' Committee, Ghent University Hospital, Gent, Belgium) approval, written informed consent was obtained from all patients. Sixty nonpremedicated outpatients, ASA physical status I or II, ages 18–65 yr, scheduled for a complete colonoscopy were randomly included in the study. Patients with a history of allergic reactions to any of the study drugs or chronically receiving opioid analgesics or sedative medication were excluded. All patients received 45 mL Fleet phospho soda for bowel preparation.

Patients received no preanesthetic medication. After consent had been obtained, but before any anesthetic or surgical interventions, successive envelopes containing allocation to one of the three treatment groups were opened by the deep sedation nurse when patients were in the preoperative holding area. Two groups received remifentanyl, one group with MCI (MCI R group, $n = 19$), the other group with TCI (TCI R group, $n = 20$). The third group received placebo (normal saline, $n = 21$). To exclude bias and maintain blinding, patients received normal saline either via MCI ($n = 11$) or TCI ($n = 10$). Except for the nurse opening the envelope and preparing the syringes, everyone was blinded. This nurse did not take part further in the study. Blinding was guaranteed by providing the remifentanyl or normal saline in coded syringes identified only with the treatment number and patient's initials. Peripheral IV access was established at the opposite arm of the noninvasive blood pressure cuff and a 500 mL crystalloid infusion was commenced. The solution of remifentanyl (20 $\mu\text{g}/\text{mL}$) or placebo and propofol were connected directly to the IV cannula using a three-way tap. In the groups receiving TCI, the target plasma concentration of the study drug (remifentanyl or normal saline) was set at 1 ng/mL . In the MCI group, the study drug infusion was started at a rate of $0.125 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for 2 min (i.e., a bolus dose of $0.25 \mu\text{g}/\text{kg}$ given over 2 min), followed by a continuous infusion of $0.05 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. For calculation of

the infusion rate, total body weight was used. The remifentanyl infusions (in the MCI group) or the target plasma concentrations (in the TCI group) were kept at the same rate/concentration throughout the procedure. Two minutes after the start of remifentanyl/placebo, propofol administration was started using plasma-controlled TCI, at an initial target concentration of 4 $\mu\text{g}/\text{mL}$ in all 3 groups. When loss of consciousness (LOC) was achieved, which was defined as unresponsiveness to both verbal and tactile stimuli, the target plasma concentration of propofol ($C_{p\text{prop}}$) was set at the same concentration as the calculated effect-site concentration of propofol ($C_{e\text{prop}}$) at which LOC occurred. When LOC was not achieved at $C_{e\text{prop}}$ 4 $\mu\text{g}/\text{mL}$, $C_{p\text{prop}}$ was increased stepwise by 1 $\mu\text{g}/\text{mL}$ until LOC, allowing plasma effect-site equilibration between every step, which could be read out in RUGLOOP II® (Demed, Temse, Belgium). Colonoscopy was then started. Propofol administration was adjusted to a level of deep sedation in which patients were no longer responsive to verbal commands and had no purposeful movements or verbal expressions of discomfort, while maintaining spontaneous ventilation without assistance. The target $C_{p\text{prop}}$ was increased by 0.5 $\mu\text{g}/\text{mL}$ every minute, if necessary, to meet this goal. If the patient was unresponsive for 3 min, the target $C_{p\text{prop}}$ was decreased by 0.5 $\mu\text{g}/\text{mL}$.

Propofol and remifentanyl were administered via a computer-assisted continuous infusion device (RUGLOOP II) to a target plasma concentration using a three-compartment model enlarged with an effect-site compartment. For propofol and remifentanyl, the pharmacokinetic-dynamic model previously published by Schnider et al.^{8,9} and Minto et al.^{10,11} were used, respectively. Calculated $C_{e\text{prop}}$ was computed to yield a time-to-peak effect¹² of 1.6 min after bolus injection, as also published by Schnider et al.^{8,9} and used clinically by Struys et al.¹³ For remifentanyl, an equilibration time constant (ke_0) of 0.595–0.007 (age 40) was applied as published by Minto et al.^{10,11} Propofol and remifentanyl infusion were administered using a Fresenius Modular DPS Infusion Pump connected to a Fresenius Base A (Fresenius Vial Infusion Systems, Brézins, France). RUGLOOP II steers the pump at infusion rates between 0 and 1200 mL/h via an RS-232 interface. RUGLOOP II was also used to record the Bispectral Index (BIS) signal (BIS XP Monitor A 2000, Aspect Medical Systems, Newton, MA) and noninvasive arterial blood pressure, heart rate (HR), end tidal carbon dioxide (EtCO_2), respiratory rate (RR), and oxygen saturation (SaO_2) (AS3 monitor, Datex, Helsinki, Finland). HR, EtCO_2 , RR, SaO_2 , and BIS were acquired every 10 s. BIS (version 4.0) was derived from the frontal electroencephalogram (At-Fpzt) using a BIS XP-Sensor® (Aspect Medical Systems, Newton, MA). Artifacts in the BIS caused by poor signal quality were automatically detected and excluded from further analysis. Arterial blood pressure was acquired every 3 min. All data were stored

on hard disk. Supplemental oxygen (5 L/min) was supplied by facemask, modified to permit monitoring of EtCO₂, RR, and respiratory pattern.

If no polyps were noticed on insertion of the scope, administration of both propofol and study drug were discontinued after the cecum was reached. If polyps were noted, propofol and study drug were discontinued after polypectomy. Duration of deep sedation was calculated as the time from the start of the study product administration to discontinuation of administration. Duration of colonoscopy was calculated from scope in to scope out.

The occurrences of any unwanted effects, such as movement, inadequate respiration, cardiovascular side effects and any adverse events or experiences, were noted. Any intervention to restore normal physiology or respiration was noted.

Immediate recovery was assessed using the Stewart Post Recovery Score (SPRS).¹⁴ The times at which the patients spontaneously opened their eyes, were able to follow the command to squeeze the investigator's hand and were able to state their date of birth were recorded.

Post hoc all respiratory data were visually inspected. Artifacts in EtCO₂ monitoring and RR caused by poor signal quality were excluded from further analysis.

Statistical Analysis and Data Presentation

Statistical power was estimated using a blinded intermittent analysis based on groups of 20 patients with apnea as the primary end-point. The applied test

Table 1. Demographic Data

	MCI R group	TCI R group	Placebo group
Number (n)	18	18	21
Sex (male/female)	8/10	6/12	5/16
Age (yr) ^a	39.4 ± 12.5	41.0 ± 13.6	39.9 ± 10.7
Height (cm) ^a	169.8 ± 9.1	169.1 ± 11.2	167.4 ± 7.1
Weight (kg) ^a	68.7 ± 12.1	66.4 ± 14.5	73.7 ± 14.5
ASA physical status (I/II)	15/3	17/1	15/6
Indication (D/C/P/UC)	13/2/3/0	15/1/2/0	13/3/3/2

MCI = manually controlled infusion; TCI = target-controlled infusion; D = diagnostic; C = Crohn's disease; P = polypectomy; UC = ulcerative colitis.

^a Age, height and weight are presented as mean ± sd, other data are shown as number of patients.

Table 2. Clinical Data

	MCI R group	TCI R group	Placebo group
LOC (s)	568 ± 147	529 ± 96	570 ± 108
Start colonoscopy (s)	674 ± 219	548 ± 124	667 ± 301
Duration of colonoscopy (s)	859 ± 298	997 ± 465	811 ± 446
Duration of deep sedation (s)	1323 ± 250	1413 ± 495	1309 ± 495
Total dose of propofol (mg)	318 ± 94	289 ± 81*	381 ± 162
Total dose of remifentanyl (μg)	40 ± 8	36 ± 9	—
BIS at LOC	65 ± 16	69 ± 15	61 ± 15

Data are presented as mean ± sd.

MCI = manually controlled infusion; LOC = loss of consciousness; TCI = target-controlled infusion; BIS = bispectral index.

* *P* = 0.056 TCI R group versus placebo group.

was a χ^2 test. If significant among the groups, the study was stopped. If not significant, a prospective power would be calculated.

All values are expressed as means ± sd. All data-sets were tested for Gaussian distribution by a Kolmogorov-Smirnov test. Between-group analysis was done using a one-way analysis of variance. If significant, *post hoc* testing was done (Bonferroni correction). Possible changes in within-group observation were tested using a repeated measures analysis of variance test. Between-group observations were analyzed using an independent sample *t*-test with Bonferroni correction for multiple comparisons. Continuous data were time-synchronized and compared every 10 s. Categorical data were analyzed using a Fisher's exact test. Kaplan-Meier survival statistics were applied on the time required to reach a maximum SPRS score.

RESULTS

Patients' demographics and clinical data were similar among groups (Tables 1 and 2). Three patients were excluded from further analysis due to protocol violation (one from the MCI R group, two from the TCI R group).

Similar times to LOC (Table 2), C_pprop at LOC (4.79 ± 1.31 μg/mL, 4.41 ± 0.63 μg/mL, and 4.59 ± 0.80 μg/mL for MCI R group, TCI R group and placebo group respectively), and BIS at LOC (Table 2) were observed in all groups.

Figure 1 shows the individual BIS and predicted C_pprop and C_eprop in the three groups. Similar overall BIS levels were found among groups. C_pprop and C_eprop were significantly different between the TCI R and the placebo group from around 10 min after starting the study and lasting until the end of the procedure. There were no significant differences in C_eprop and C_pprop between the MCI R group and the two other groups.

Figure 2 shows the individual calculated plasma (C_premi) and effect-site concentrations of remifentanyl (C_eremi). Although the bolus dose of remifentanyl was given over 2 min in the MCI group, a clear overshoot in C_premi was noted. Large interpatient variability can be observed in the MCI R group for both C_eremi and C_premi.

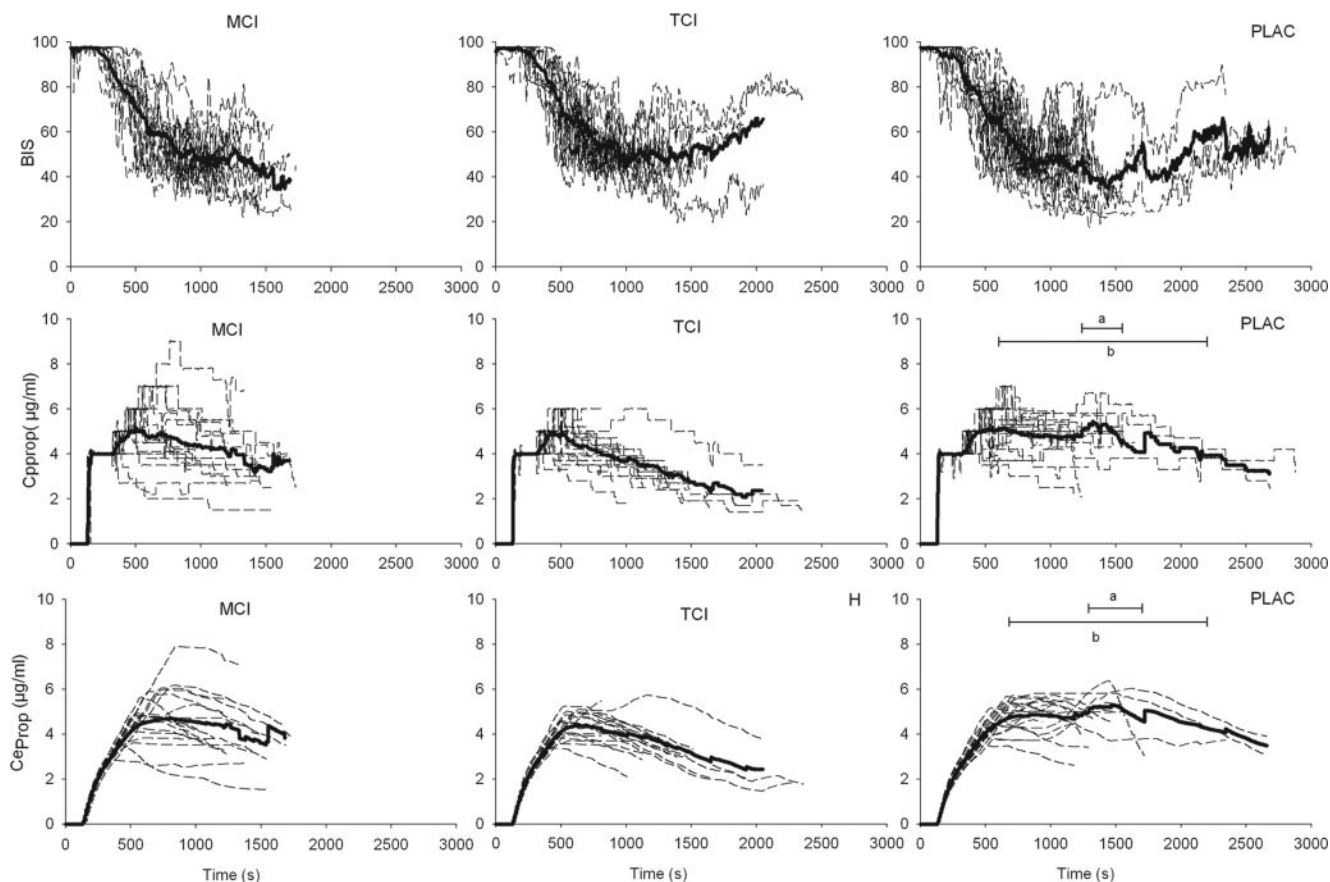


Figure 1. Individual bispectral index (BIS) and predicted plasma and effect-site concentrations of propofol. MCI = manual infusion group; TCI = target-controlled infusion group; PLAC = placebo group. ^a = $P < 0.05$ between MCI and PLAC and ^b = $P < 0.05$ between TCI and PLAC.

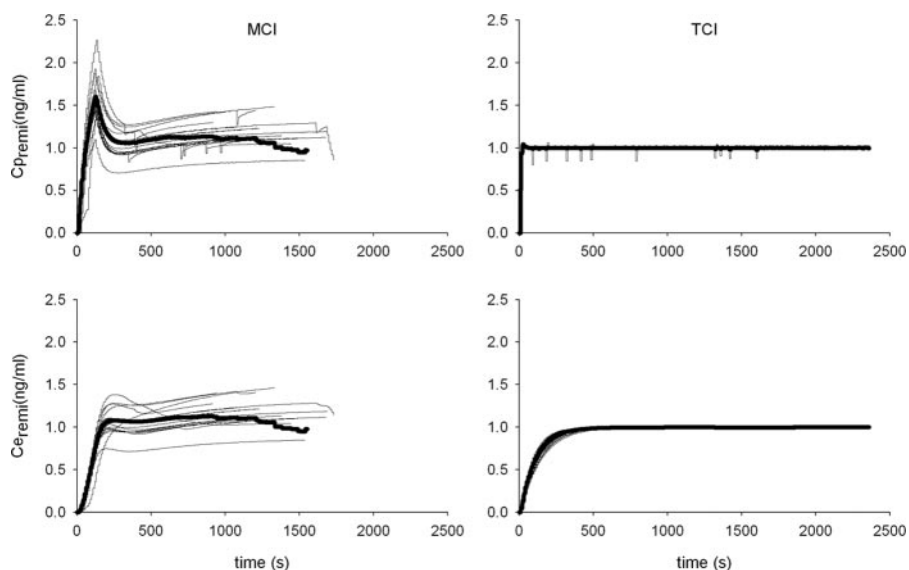


Figure 2. Individual predicted plasma and effect-site concentrations of remifentanyl. MCI = manual infusion group; TCI = target-controlled infusion group.

There was no difference in systolic and diastolic blood pressure and in SaO_2 among groups. HR was significantly more rapid in the placebo group compared to the TCI R group starting at approximately 10 min after the study drug was initiated and lasting throughout the procedure.

Untoward events are shown in Table 3. Significantly more patients in the placebo group showed

movement, cough and hiccup, which transiently interfered with the examination. More respiratory side effects were found in both remifentanyl groups. Apnea was significantly more frequent in the MCI R group compared to the TCI R group. Respiratory side effects were managed by chin lift/jaw thrust in all cases of obstructive respiration, and with gentle assisted mask and bag ventilation to prevent desaturation until

Table 3. Events

	MCI R group (n = 18)	TCI R group (n = 18)	Placebo (n = 21)	P*
Purposeful movement	2	5	10	0.044
Nonpurposeful movement	1	4	4	0.342
Excitatory movement	0	0	3	0.066
Obstructive respiration	9	10	2	0.008
Bradypnea (RR <6 breaths/min)	8	5	0	0.009
Apnea	8	2	0	0.003
Cough	0	0	4	0.025
Hiccup	0	0	3	0.066
Drowsiness	5	2	3	0.373
Nausea/vomiting	0	0	0	1.000

Data are shown as number of patients.

MCI = manually controlled infusion; TCI = target-controlled infusion; RR = respiratory rate.

* P-value between the three groups obtained with a χ^2 test as "group * event."

spontaneous ventilation returned in all cases of apnea. Time of onset of apnea was 414 s and 889 s for the 2 patients in the TCI R group, and ranged from 373 s to 1333 s in the 8 patients of the MCI R group.

C_eprop at recovery of consciousness and recovery times were comparable among the three groups (Table 4). Survival statistics showed that the time to reach a maximum SPRS did not differ among groups.

Post hoc analysis of the pharmacokinetic data revealed significant differences among the groups. Time to reach C_eremi of 0.95 ng/mL (95% of the target concentration) was 162.65 ± 33.93 s in the MCI R group versus 325.78 ± 56.41 s in the TCI R group (P < 0.05). Maximum C_premi (C_premi_{max}) and C_eremi (C_eremi_{max}) were significantly higher in the MCI R compared to the TCI R group. Maximum C_eprop (C_eprop_{max}) was significantly lower in the TCI R group compared to the placebo group (Table 5).

When subdividing the MCI R group into patients who experienced apnea (n = 8) versus patients who did not (n = 10), we found a significantly higher C_premi_{max} in the apnea group (1.797 ± 0.324 ng/mL vs 1.490 ± 0.193 ng/mL in the no apnea group). C_eremi_{max} had a tendency to be higher in the apnea group (P = 0.07). C_eprop_{max} was not significantly

Table 4. Recovery Data

	MCI R group	TCI R group	Placebo group
C _e prop at ROC (μg/mL)	1.80 ± 0.88	1.69 ± 0.48	2.13 ± 0.56
Time to open eyes (s)	350 ± 168	240 ± 116	302 ± 138
Time to follow command (s)	345 ± 152	260 ± 126	300 ± 117
Time to state date of birth (s)	348 ± 151	262 ± 125	304 ± 120

Data are presented as mean ± sd.

MCI = manually controlled infusion; TCI = target-controlled infusion; ROC = recovery of consciousness; C_eprop = effect-site concentration of propofol.

Table 5. Maximum Predicted Plasma and Effect-Site Concentrations

	MCI R group	TCI R group	Placebo group
C _p remi _{max} (ng/mL)	1.627 ± 0.296	1.047 ± 0.110*	—
C _e remi _{max} (ng/mL)	1.223 ± 0.160	0.999 ± 0.001*	—
C _e prop _{max} (μg/mL)	4.957 ± 1.208	4.520 ± 0.666†	5.218 ± 0.706

Data are presented as mean ± sd.

MCI = manually controlled infusion; TCI = target-controlled infusion; C_eremi_{max} = maximum effect-site concentrations of remifentanyl; C_premi_{max} = maximum plasma concentrations of remifentanyl; C_eprop_{max} = maximum effect-site concentration of propofol.

* P < 0.05.

† P < 0.05 TCI R group versus placebo group.

different (4.70 ± 1.24 μg/mL vs 5.16 ± 1.20 μg/mL in respectively the apnea and the no apnea group).

DISCUSSION

This study was conducted to investigate two questions: first, if the advantages of the addition of remifentanyl to propofol in spontaneously breathing patients surpasses the disadvantages of the combination of these two products, and second, if administration of remifentanyl via TCI optimizes drug delivery, resulting in a safer and more reliable technique for coadministration of propofol and remifentanyl.

We found that the addition of remifentanyl to propofol resulted in less movement, hiccup and cough and thus the combination of remifentanyl and propofol offered better conditions for colonoscopy than propofol used as a single drug. We also found that administering remifentanyl via TCI offered further benefit compared to manual administration of remifentanyl, as remifentanyl TCI reduced propofol requirements and decreased the incidence of respiratory depression.

Previous studies showed that a single drug is unable to manage amnesia, analgesia, and immobility during procedural deep sedation.¹⁵ This was confirmed in our study, in which movement, cough and hiccup in the group receiving only propofol frequently interfered with the examination, making the conditions for colonoscopy less beneficial. This proves the difficulty of managing noxious stimuli when only using propofol. We hypothesized that the combined use of propofol-remifentanyl might result in optimal control of all components of the anesthetic state during procedural deep sedation. When coadministering remifentanyl to propofol, we found a decreased incidence of somatic responses. Unfortunately, remifentanyl is a potent ventilatory depressant. Nieuwenhuijs et al.⁵ studied the remifentanyl-propofol interaction on cardiorespiratory control using the technique of response surface modeling. They observed strikingly synergistic respiratory depression when remifentanyl and propofol are combined, even in low concentrations. When observing the ventilation-CO₂ response curve, the combined administration of remifentanyl

and propofol yielded both a rightward shift of the response curve (typical μ -opioid effect) and a reduction in the slope of the curve (typical effect of a hypnotic/sedative). We hypothesized that administration of remifentanyl via TCI would optimize drug delivery, resulting in a lower incidence of respiratory side effects.

TCI has been developed to optimize drug delivery by targeting a specific therapeutic drug concentration in a specific body compartment. The drug's typical pharmacokinetic behavior was first characterized from clinical pharmacology studies in widely different patient populations and implemented physiologic or disease state covariates. All these data are preprogrammed into the multi-compartmental pharmacokinetic model of the TCI system, minutely describing the distribution and elimination of the drug within the body. The TCI system calculates the infusion rate to achieve and maintain the defined target concentration as fast and accurately as possible without overshoot. Because the drug accumulates in the body, the system frequently recalculates the appropriate drug dosage and updates the infusion rate, enabling a steady-state concentration of drug. In other words, TCI systems reduce both time-dependent variability (by continuously updating the infusion rate) and interpatient variability (by implementing the effect of covariates on pharmacokinetics). TCI systems use complex mathematical models to compute the drug dosage. It is impossible to perform these complex calculations and control drug administration with the same accuracy when using MCI systems.⁶

There are no studies demonstrating a clear patient benefit when using remifentanyl through TCI instead of manually controlled remifentanyl administration. Obviously, to evaluate this, we needed comparable remifentanyl concentrations in the two study groups. Therefore, we first performed pharmacokinetic simulations, using the RUGLOOP II program, to ensure similar calculated remifentanyl effect-site concentrations, as well as a similar concentration trajectory in the two remifentanyl groups. A bolus dose of 0.25 $\mu\text{g}/\text{kg}$ given over 2 min, followed by a continuous infusion of 0.05 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ gave the best approximation of the target $C_{e\text{remi}}$ of 1 ng/mL. As shown in Figure 2, the simulation was very accurate since the mean $C_{e\text{remi}}$ approached 1 ng/mL in the MCI R group.

Despite our efforts to imitate the TCI profile as closely as possible, overshoot, interpatient variability, and accumulation of remifentanyl was noted in the MCI group. This is clearly depicted in Figure 2. *Post hoc* analysis of our pharmacokinetic data also revealed that $C_{p\text{remi,max}}$ and $C_{e\text{remi,max}}$ were significantly higher in the MCI R group compared to the TCI R group.

We realize that concentrations reported by the TCI system are predicted, not true concentrations, and therefore the difference between the MCI R and the TCI R

group is a function of the pharmacokinetic-dynamic model used. We did not measure remifentanyl plasma concentrations, since the pharmacokinetic-dynamic model we used has been demonstrated as adequately accurate in predicting plasma and effect-site concentrations of remifentanyl.^{10,11} However, higher variability, overshoot and accumulation of drug in the MCI group compared to the TCI group is well known and was not surprising, since, as mentioned before, TCI evaluates the complexity of the drug pharmacokinetic characteristics, which manual administration regimen cannot.⁶

In our study, it is remarkable that, although we designed our MCI group to receive virtually the same effect-site concentration as our TCI group, we found significant differences. We found a significantly higher incidence of apnea of the MCI R group compared to the TCI R group (Table 3). We also found that remifentanyl administered via TCI resulted in a decrease in propofol requirements (Table 5, Fig. 1).

It is possible that the difference in incidence of apnea is solely attributable to a dosing difference. When comparing patients who experienced apnea versus patients who did not, $C_{p\text{remi,max}}$ was significantly higher in the apnea group. If the difference in incidence of apnea was indeed due to the dosing difference, this means that the pharmacokinetic inaccuracy, which is inherent to manual controlled infusions, has important pharmacodynamic repercussions. This is especially important in situations in which there is little room for error, as is the case with remifentanyl in spontaneously breathing patients.

Another explanation for the difference in apnea between the MCI R and the TCI R group could be the more bolus type of administration of remifentanyl at the beginning of the administration in the MCI R group. In the MCI R group, $C_{e\text{remi}}$ of 0.95 ng/mL was reached twice as fast as in the TCI R group. One would suppose that, if the difference was due to this more rapid bolus administration in the MCI R group, the major difference between the groups would have been at induction. However we found no difference in time of onset of apnea between the two groups. One reason could be, as stated by Bouillon et al.,¹⁶ that RR is not a good indicator for respiratory depression. They state that an increase in tidal volume variability is a better predictor of respiratory depression than decreased RR. Since this was a study performed in a clinical situation the tools to measure tidal volume variability were not available.

Besides the difference in incidence in apnea, we also found a difference in propofol concentrations among the study groups. $C_{p\text{prop}}$, $C_{e\text{prop}}$, and $C_{e\text{prop,max}}$ were significantly lower in the TCI R group compared to the placebo group, whereas the propofol concentrations in the MCI group did not differ from the two other groups. According to the study protocol, the target $C_{p\text{prop}}$ was decreased by 0.5 $\mu\text{g}/\text{mL}$ if the patient was unresponsive for 3 min. In Figure 1, we depicted the $C_{p\text{prop}}$ of all patients individually. From this figure,

it is clear that in the TCI group the decrease of the propofol target concentration is consistent, whereas in the MCI group decreasing the propofol target concentration was more burdensome. We presume that this was due to the large interindividual variability in remifentanyl concentrations in the MCI group making deep sedation far less manageable.

In conclusion, we have shown that the addition of remifentanyl to propofol provides more stable anesthetic conditions compared with propofol used as a single drug. Administering remifentanyl via TCI during spontaneous ventilation results in a decrease in propofol dosing and in a lower incidence in apnea compared to remifentanyl administered via MCI.

Since the combination of propofol and remifentanyl, even in TCI, still results in strikingly synergistic respiratory depression, careful monitoring of respiratory function and appropriate skills in the recognition and treatment of inadequate respiration remain mandatory.

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