

ORIGINAL ARTICLE

Women awaken faster than men after electroencephalogram-monitored propofol sedation for colonoscopy

A prospective observational study

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BACKGROUND Sedation for colonoscopy using intravenous propofol has become standard in many Western countries.

OBJECTIVE Gender-specific differences have been shown for general anaesthesia in dentistry, but no such data existed for gastrointestinal endoscopy.

DESIGN A prospective observational study.

SETTING An academic teaching hospital of Hannover Medical School.

PATIENTS A total of 219 patients (108 women and 111 men) scheduled for colonoscopy.

INTERVENTION Propofol sedation using electroencephalogram monitoring during a constant level of sedation depth (D0 to D2) performed by trained nurses or physicians after a body-weight-adjusted loading dose.

MAIN OUTCOME MEASURES The primary end-point was the presence of gender-specific differences in awakening time (time from end of sedation to eye-opening and complete orientation); secondary outcome parameters analysed were

total dose of propofol, sedation-associated complications (bradycardia, hypotension, hypoxaemia and apnoea), patient cooperation and patient satisfaction. Multivariate analysis was performed to correct confounding factors such as age and BMI.

RESULTS Women awakened significantly faster than men, with a time to eye-opening of 7.3 ± 3.7 versus 8.4 ± 3.4 min ($P = 0.005$) and time until complete orientation of 9.1 ± 3.9 versus 10.4 ± 13.7 min ($P = 0.008$). The propofol dosage was not significantly different, with some trend towards more propofol per kg body weight in women (3.98 ± 1.81 mg versus 3.72 ± 1.75 mg, $P = 0.232$).

CONCLUSION The effect of gender aspects should be considered when propofol is used as sedation for gastrointestinal endoscopy. That includes adequate dosing for women as well as caution regarding potential overdosing of male patients.

TRIAL REGISTRATION ClinicalTrials.gov (Identifier: NCT02687568).

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Introduction

Gastrointestinal endoscopy and, under special surveillance, colonoscopy are performed under sedation, using propofol as the main recommended sedative due to its excellent pharmacological profile offered by a short half-life.^{1–3} Higher postprocedure patient satisfaction is achieved with propofol than traditional sedation for

colonoscopy.⁴ In addition, both time to onset of sedation and recovery time are shorter with propofol than with traditional sedation.^{4,5}

However, it is well known that, during propofol sedation for gastrointestinal endoscopy, cardiorespiratory

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side-effects may occur in up to 11% of patients regarding hypoxaemia and 12.5% regarding hypotension in association with colonoscopy.^{4,5} Therefore, monitoring of the vital signs [e.g. heart rate (HR), blood pressure (BP) and oxygen saturation] is required by many national guidelines on sedation for gastrointestinal endoscopy.^{1,6,7} To date, extended monitoring devices (e.g. capnography or neuromonitoring using the bispectral index or electroencephalography) have not been recommended routinely for gastrointestinal endoscopy.^{1–3} However, a first trial of our working group has shown that more effective titration of propofol dose associated with faster patient recovery under a continuous sedation stage of D0 to D2 can be achieved in the context of endoscopic retrograde cholangiopancreatography (ERCP).⁸

There is some data regarding gender differences for propofol dose and recovery time when comparing men and women,^{9,10} showing that women might need a higher dose of sedative for general anaesthesia due to faster recovery times, but no data exist on gender differences when using propofol with an intermittent bolus injection technique for different gastrointestinal procedures.

The aim of the current study was to examine whether the extent of gender differences in the recovery time after sedation with propofol during colonoscopy may be detected by the use of electroencephalogram (EEG) monitoring.

Patients and methods

This was a prospective observational trial. Patient enrolment started in May 2014 and was concluded in June 2016. Patients aged more than 18 years who were scheduled for colonoscopy for diagnostic and therapeutic colonoscopy at our department were eligible for the study. For all patients, demographic and clinical data as well as risk factors for sedation, such as age, height, weight, BMI, alcohol and/or nicotine abuse, American Society of Anesthesiologists' (ASA) physical status and Mallampati classification were recorded (Table 1).

Patients from whom informed consent could not be obtained due to an emergency situation (lower gastrointestinal bleeding), patients with ASA class 4 or 5, those with pre-existing hypoxaemia ($SpO_2 \leq 90\%$), hypotension (SBP < 90 mmHg) or bradycardia (HR < 50 bpm) before the beginning of the procedure, as well as pregnant women and patients aged less than 18 years, were excluded.

Ethical approval for this study (Ethical Committee No. 4439-12) was provided by the Ethical Committee of the Medical Faculty Ruhr University Bochum, Bochum, Germany (Chairperson Prof Dr M. Zenz) on 16 January 2013. The study was also registered at ClinicalTrials.gov (Identifier: NCT02687568).

Table 1 Demographics and risk factors for sedation

	Men, n = 111		Women, n = 108		P	Effect
	Mean	SD	Mean	SD		
Age (years)	64.8	15.1	66.9	16.0	.204	-0.099
Height (cm)	175.9	6.4	164.1	6.8	.001	1.793
Weight (kg)	82.5	15.75	70.1	15.3	.001	0.459
BMI (kg m ⁻²)	26.6	4.7	26.0	5.4	.065	0.144
	n	n	P	Effect		
Alcohol abuse	13	4	.041	0.291		
Nicotine abuse	24	19	.499	0.775		
ASA						
1	45	37				
2	55	63	.421	0.090		
3	11	8				
Mallampati						
I	34	36				
II	68	69	.246	0.118		
III	9	3				

ASA, American Society of Anesthesiologists' physical status. Bold values signifies statistically significant.

All patients were monitored for clinical signs of respiratory abnormalities. HR, pulse oximetry and ECG changes in patients with known heart disease were continuously assessed. Noninvasive BP measurement was measured automatically at 3-min intervals. Any abnormal events detected on pulse oximetry, pulse rate or BP measurements were crosschecked for any mechanical issues related to devices and sensors. A small preamplifier and a unit for analysis and display of EEG data were used (Narcotrend; MT MonitorTechnik, Bad Bramstedt, Germany) to assure a predefined sedation level in all patients. The EEG was recorded by means of three self-adhesive ECG electrodes placed on the forehead of the patient. The system performed automated analysis of EEG segments of 20-s durations (20-s epochs). After extensive artefact analysis, the EEG epochs are automatically classified by multivariate statistical procedures by using a scale from A (awake) to F (very deep sleep) with 14 substages¹¹ (adopted from a visual EEG classification system proposed by Kugler¹²). The algorithm includes adaptations for age-related EEG changes from childhood to old age and was developed by one of the co-authors (BS).¹¹ Validation studies have shown that the Narcotrend provides an accurate assessment of hypnotic depth compared with conventional EEG analysis during propofol sedation.^{13,14} Before the current study, this device was used during 85 interventional endoscopic procedures, and the sedation levels D0 to D2 (moderately deep sleep according to Krugler¹²) were found to be optimal in regard to patient tolerance and avoidance of cardiorespiratory side-effects.¹³ EEG monitoring was used in this trial, as it enables more effective titration of propofol dosage for sedation during endoscopy, which had already been shown by our working group in a randomised trial when used for ERCP.⁸ Therefore, EEG stages D0 to D2 were also considered the target levels in the current trial. Adjusting the level of deep sedation or anaesthesia to a predefined EEG value is

often associated with a time delay of 20 to 145 s.¹⁵ In addition, trials have determined that the Narcotrend monitor cannot properly determine the transition from alertness to unconsciousness.^{16,17} The use of propofol sedation often leads to a level of deep sedation (defined as respiratory function mildly restricted, according to the ASA).^{1,6} Therefore, all our patients were evaluated clinically before a decision for propofol injection was made to ensure that stages of deep sedation were not exceeded because of the known time lag to translate variable plasma concentrations into a detectable EEG signal. The level of general anaesthesia, defined by the ASA as spontaneous breathing inadequate, orotracheal intubation or laryngeal mask necessary was not the target in our patients, who all breathed spontaneously.

A non-anaesthesiologist sedation technique with intermittent propofol bolus injections reflecting the most commonly used sedation regimen for gastrointestinal endoscopy (performed by an independent physician experienced in intensive care and resuscitation or a trained nursing staff depending on daily availability) was applied to achieve and maintain an adequate level of sedation defined as a Narcotrend stage of D0 to D2. All patients received, independent of their sex, a loading dose of propofol (Propofol 1%; Fresenius Kabi, Bad Homburg, Germany) adjusted to body weight (40 mg at <70 kg body weight or 60 mg at \geq 70 kg body weight) given before the endoscopic procedure started. In patients of advanced age or with pre-existing co-morbidities, lower initial propofol doses were given (e.g. 20 mg). After the initial administration of sedatives, an adequate sedation level was maintained by the injections of repeated doses of propofol (10 to 20 mg). All vital signs, including BP, oxygen saturation and pulse rate were checked before administering any sedative medication.

The duration of the procedure was defined as the time between administration of the first dose of propofol and withdrawal of the endoscope from the mouth. Patient cooperation during endoscopy was rated by the endoscopist on a numerical analogue scale (1 to 10) at the end of the procedure. The time until the patient opened the eyes for the first time after endoscopy was recorded, as well the time when patients attained full recovery. At this stage, they were asked to rate their satisfaction with the sedation on a numerical analogue scale (1 to 10) and were then discharged from the endoscopy unit to an inpatient ward.

The primary outcome parameter was the mean recovery time (eye opening and full orientation) after sedation in stage D0 to D2 using EEG monitoring.

The secondary outcome measures were: incidence of hypoxaemia (defined as a decrease of SpO₂ to <90%); further vital parameters such as apnoea (no breathing activity on capnography for >15 s), bradycardia (HR < 50 bpm) or hypotension (SBP < 90 mmHg) and

any need for assisted ventilation (as an unwanted complication). Patients' satisfaction and cooperation were rated by an independent observer after the procedure.

The sample size calculation was performed using the primary end-point, the mean recovery time after sedation in stage D0 to D2 using EEG monitoring (Narcotrend) considering gender differences. The case number of patients was determined using a nomogram¹⁸ as 85 patients in each group. The aim was to achieve statistical significance when comparing both groups of patients using the *t* test at a power of 95% with a two-sided significance level of *P* less than 0.05. To compensate for expected protocol violations or drop-outs, 100 patients were included in each group.

Statistical analysis

We report mean and SD for continuous data and absolute as well as relative frequencies for categorical data. For comparisons of two (unpaired) groups, the *t* test/Welch's test was used if the normality hypothesis could not be rejected by the Shapiro–Wilk test. For non-Gaussian samples, preference was given to the Wilcoxon–Mann–Whitney test. In the case of group comparisons of categorical data, we applied Fisher's exact test. We investigated whether the group effect remained significant when taking the potential effect of additional covariates (ASA physical status, BMI, propofol dosage per kg body weight, alcohol abuse) into account. The modelling approach chosen for this analysis was an analysis of covariance (ANCOVA) and multiple regression type model for categorical and numerical covariates, respectively. For all tests, we considered a two-tailed *P* value of less than 5% statistically significant.

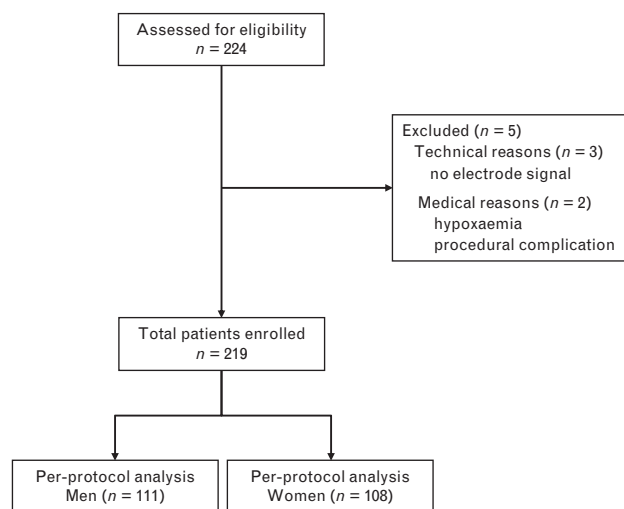
For all between-group comparisons, we report the respective effect sizes as well. More precisely, for continuous data, we provide Cohen's *d* and Cliff's δ for Gaussian samples and samples violating the normality assumption, respectively. In the categorical case, we calculated the effect size in terms of odds ratios for 2 \times 2 frequency tables, and used the Φ coefficient for tables of higher dimension. We carried out all statistical analysis with R 3.1.2 (www.r-project.org).

Results

A total of 224 patients were enrolled into the study. However, three patients dropped out for a technical reason (no electrode signal), and two patients dropped out for medical reasons (hypoxaemia after propofol sedation during colonoscopy or a procedural complication). Data from 219 patients (111 men and 108 women) were evaluated (Fig. 1).

Demographic and clinical data as well as risk factors for sedation for men and women are shown in Table 1. The study population age for men was 64.8 ± 15.1 years and 66.9 ± 16.0 years for women. The only differences among

Fig. 1



Study flow diagram.

the quantitative variables were height and weight, which were expected. The BMI values were similar in both gender groups. For qualitative variables, only the proportion of alcohol abuse differed slightly with gender, which was also expected.¹⁹ ASA physical status, Mallampati score and nicotine abuse were similar in men and women. The durations of the procedure and of the sedation were also similar. The total amount of propofol required for each patient was expressed in mg and proportional to the body weight (propofol in mg per kg body weight). Also, with regard to both the total amount of propofol and the amount of propofol proportional to body weight required per procedure, there were no statistically significant differences between women and men (Table 2). The average dose of propofol proportional to the body weight was higher for women.

The results of the primary end-points, comparing the time required until eye opening and orientation, respectively, for men and women, are shown in Table 3. On average, men needed 8.4 ± 3.4 min for eye opening, whereas women required only 7.3 ± 3.7 min. For orientation, the results were similar; men needed 10.4 ± 3.7 min but women only 9.1 ± 3.9 min. For both variables, the difference between men and women was significant ($P < 0.01$). The difference between men and women remained significant when including the

covariates ASA physical status, BMI, propofol dosage per kg body weight, and alcohol abuse, age, height and weight into an ANCOVA or multiple regression type model (data not shown). The response variables (time until eye opening/orientation) were log-transformed in order not to violate the normality hypothesis.

The level of sedation measured in terms of propofol per kg of body weight had no significant effect on the time until eye opening, but is significant at the 5% level for the time until orientation. However, the gender effect remains highly significant in both cases, and the effect size of the gender effect does not change significantly.

The variables BMI, height and weight had a significant effect when included as secondary covariate for the time until eye opening as the response variable. Moreover, BMI, propofol per kg, height and weight showed a significant effect when included as secondary covariate for the time until orientation as response variable. Nevertheless, in all cases the gender effect remained significant, and the effect size did not change substantially.

Regarding the secondary end-points (hypoxaemia, hypotension and bradycardia), as well as patient cooperation and patient satisfaction, no differences were observed between men and women (Tables 4 and 5).

Discussion

To what extent gender-specific factors should be considered in sedation or anaesthesia is currently the subject of only a few studies, mainly focused on surgical procedures.^{9,10,20} However, this approach is particularly important with regard to individualised therapy of patients, which, in addition to age and BMI, increasingly also takes gender into account to adapt to the needs of men and women.

The aim of the current study was to examine if and to what extent gender differences in the recovery time from propofol sedation during colonoscopy may be detected by the use of EEG monitoring to maintain a constant level of sedation. As expected and previously reported in other studies,^{19,21} men and women in our trial differed in height and weight and the rate of alcohol abuse, which differed slightly also in our trial in favour of the men, but neither affected the gender findings nor was a predictive factor.

The main difference between male and female patients detected in our trial was a significantly shorter time to

Table 2 Descriptive statistics of procedures

	Men, n = 111		Women, n = 108		P
	Mean	SD	Mean	SD	
Procedure time (min)	25.4	13.0	24.9	10.9	.695
Sedation duration (min)	23.8	13.9	23.2	12.3	.911
Total propofol dose (mg)	301.1	140.7	275.2	128.1	.135
Propofol dose (mg kg ⁻¹)	3.72	1.75	3.98	1.81	.232

Table 3 The primary end-point: times to eye opening and complete orientation

	Men, n = 111		Women, n = 108		P	Effect
	Mean	SD	Mean	SD		
Time to eye opening (min)	8.4	3.4	7.3	3.7	.005	0.218
Time to full orientation (min)	10.4	3.7	9.1	3.9	.008	0.206

Bold values signifies statistically significant.

open the eyes and to full orientation after the procedure for women, although female patients needed slightly more propofol than men.

These results are compatible with the data from Wilhelm *et al.*,²⁰ who investigated the influence of gender on propofol consumption and recovery times in minor orthopaedic surgery. In that study, 60 male and 60 female patients with an average age of 44 years randomly received propofol–remifentanyl anaesthesia by target-controlled infusions (TCI) either controlled by EEG monitoring or only by clinical parameters (standard group). In the standard group, consumption of propofol was nearly identical for male and female patients, but recovery times were significantly longer in the male group. However, in EEG-guided groups, propofol consumption was less for male patients, whereas recovery times were slightly longer than in female patients. In addition, female patients needed higher propofol TCI concentrations to reach the same EEG values compared with men.

A further study by Haensch *et al.*¹⁰ retrospectively examined the amount of propofol required in 239 women and 417 men with a mean age of 52 years, who underwent various surgical procedures under EEG-monitored anaesthesia with remifentanyl and propofol. The authors observed that a significantly higher dose of propofol was needed to maintain the predefined narcotic stage in women. However, the time to extubation was significantly shorter in women than in men. These results correspond with our observation on the primary end-point (waking time), which was also significantly shorter in women than in men.

It may be argued that maintaining a constant propofol plasma concentration with intermittent bolus injections is impossible, that it is probable that the patient was constantly on an 'up and down' curve for propofol concentration and that a TCI system would probably be more accurate in keeping the patients at a constant propofol

concentration. However, such an argument can neither be excluded nor confirmed. Although administration of propofol by infusion pump is currently the method most often used to maintain total intravenous anaesthesia worldwide, there are only a few studies of its use during sedation for endoscopy. A randomised, comparative trial by our working group evaluating propofol administration techniques (infusion pump versus intermittent bolus administration) during interventional endoscopy showed no relevant difference regarding the efficacy of sedation or in terms of adverse reactions.²² Total propofol doses were comparable and both sedation regimens allowed good and nearly identical controllability of propofol sedation. However, recovery time was significantly slower and hypotension tended to occur more often in the infusion pump group. Moreover, in that group, administration of additional propofol boluses was needed in 10% of patients due to involuntary patient movements (median of four boluses per patient with a range of two to six boluses). The advantage of the individual control of propofol sedation with bolus injection (reflecting daily routine in most countries) is demonstrable in endoscopic procedures with rather short interventions (procedure time in the current study averaged 23 min), compared with the regularly used TCI for long-term surgical interventions under general anaesthesia.

Comparing our data, we also noticed a higher consumption of propofol. However, the additional consumption per kg body weight of women in total was relatively low ($3.72 \pm 1.75 \text{ mg kg}^{-1}$ in men and $3.98 \pm 1.80 \text{ mg kg}^{-1}$ in women) and not statistically significant. This may be a consequence of the older patient group in our trial. In the study by Haensch *et al.*,¹⁰ a decrease in propofol dosage of $0.46 \text{ mg kg}^{-1} \text{ h}^{-1}$ per decade of life in women and $0.28 \text{ mg kg}^{-1} \text{ h}^{-1}$ in men was reported. The relatively high age of our study population, with a mean age of 65 years, represents the mean population treated in our hospital and in other primary and secondary care hospitals across Germany.²³

Table 4 Secondary end-points: hypoxaemia, increase in oxygen flow, hypotension and bradycardia

	Men n	Women n	P	Effect
Hypoxaemia (SpO ₂ < 90%)	2	4	.441	2.089
Increased oxygen flow (>2 l min ⁻¹)	15	9	.281	0.583
Assisted ventilation	1	0	1.000	0.000
Hypotension (SBP < 90 mmHg)	27	15	.059	0.503
Bradycardia (<50 bpm)	3	2	1.000	0.680

Table 5 Descriptive statistics of patient cooperation and patient satisfaction

	Men		Women		P
	Mean	SD	Mean	SD	
Cooperation (VAS 1 to 10)	9.3	1.3	9.2	1.0	.190
Satisfaction (VAS 1 to 10)	9.5	0.9	9.5	0.8	.674

VAS, visual analogue scale.

Maeda *et al.*⁹ investigated 125 patients undergoing dental implant-related surgery with intravenous propofol sedation under EEG monitoring and showed that women required a higher rate of propofol infusion to maintain a predefined sedation level. However, they found that the age correlated significantly with the primary end-point (total propofol amount), but was not an independent prediction value and a disturbance factor when looking at gender. In contrast, in our trial, eye opening and orientation times remained significantly different between sexes even if co-variated with height and body weight.

Both in our study ($n=219$) and in the study by Maeda *et al.*⁹ ($n=125$), the number of patients was much lower than in the study by Haensch *et al.*¹⁰ ($n=656$), which might be the reason for the undetectable correlation between age, sex and propofol dose due to a potential lack of power. The effect seen by Haensch *et al.*,¹⁰ suggesting that women needed more sedative, could not be repeated but our findings are generally comparable regarding a faster recovery time in women.

Our results might be best explained by gender-dependent differences in pharmacokinetics and pharmacodynamics for opioids, muscle relaxants and intravenous anaesthetics as demonstrated in previous studies,^{24,25} which also specifically investigated propofol. The faster recovery time may be the result of a lower plasma concentration of propofol in 10% of women, as reported in a study by Vuyk *et al.*²⁶ It was also shown in a study by Hoymork and Raeder²⁷ that, after the interruption of propofol administration, the propofol plasma concentration in women fell significantly faster than in men ($P=0.001$). This observation was further investigated in a study by Choong *et al.*²⁸ dealing with the influence of sex on propofol metabolism. Significant differences were found in the concentration of glucuronidated degradation products in women and men under continuous propofol TCI.

This data was confirmed by a study by Loryan *et al.*,²⁹ in which significantly higher concentrations of glucuronidated propofol were measured in females. The CYP2B6 concentration (a degradation enzyme of propofol which is one of the cytochrome P450 enzymes responsible for the oxidative metabolism of drugs) was 1.9-fold higher in the liver of women than in men ($P=0.035$).

Regarding the overall dose of propofol, our study reveals a trend towards higher doses in women (based on the dose per kg body weight), although the difference was NS. This difference is more pronounced in published studies of younger patients.^{9,10,20} This may have been due to the age-dependent and gender-dependent sensitivity to propofol reported by Haensch *et al.*¹⁰ Both sexes need smaller doses in old age, but this effect is more pronounced in women as they age. Maeda *et al.*⁹ could not establish a statistical correlation between age and sex in their trial. However, in our study, the average age of

patients (65 years) is significantly higher than in the studies cited.^{9,10,20}

A possible explanation for the higher dosages is the higher fat content of the total body weight in women, with lower total body water content.³⁰ The very high lipophilicity of propofol leads to a higher distribution volume per kg of body weight and therefore a lower plasma concentration, which must be compensated with a higher dosage. However, these effects are not pronounced in the 'steady-state' phase in a continuous infusion, such as those used in anaesthesia and intensive care medicine, as a compensation of the concentration has already taken place in the different compartments.²⁰

Decisive here is the elimination of propofol and thus the differences in the rate of metabolism. This differs in the context of sedation in gastrointestinal endoscopy with the administration of propofol boluses. There may not be a 'steady-state' in the brevity of time, and the effects of the distribution of propofol on the increased fat content in women might be important.

In addition, the very high inter-individual variation of the effect of propofol should be considered in view of possible implications of the recovery time and higher total amount of propofol for sedation in women's endoscopy.³¹ Pley *et al.*³² have discussed a possible reduction of propofol of 30 to 40% for sedation of men. As stated in their survey article from 2003, men seem to be more sensitive to propofol than women.

Our study does have some limitations. Mixed clinical impressions and Narcotrend observations gave a good and reliable impression of the patients undergoing colonoscopy. They offered objective judgement on awokeness. However, other patient medication was not fully assessed and could have had an influence on the study outcomes. In light of the population age, typical gender-specific CYP-altering contraceptive medication could be excluded, but antihormonal treatment could not.

A sole focus on the Narcotrend monitor may have meant that both sexes were not at the same level of sedation at the end of the procedure. This might theoretically result in slight differences in recovery. Therefore, according to the definition of the ASA, all patients were clinically held in a level of deep sedation. The observed gender effect might not exist in all ages. There could be a different or stronger finding in a younger population, or in critically ill patients. Other, yet unknown, factors, including environmental and social factors (e.g. distress before colonoscopy), might have had an influence on our observation. Current findings³³ suggest that social and environmental factors have an impact and should be considered in further trials.

Conclusion

To allow the most secure and effective sedation for gastrointestinal endoscopy to be individualised to each

patient, the consideration of gender as well as age and body weight could become more important in the future. The results of the prospective observation study presented here with significantly different wake-up times between men and women (with a slightly increased propofol requirement of the women in relation to body weight) suggest that gender-specific pharmacokinetics must also be considered during sedation in gastrointestinal endoscopy. That includes adequate dosing for women as well as caution regarding overdosing male patients.

However, in this context, further prospective, gender-sensitive clinical trials with a larger population of patients and additional questions (e.g. social and environmental) are needed.

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References

- Dumonceau JM, Riphaus A, Schreiber F, et al. Nonanesthesiologist administration of propofol for gastrointestinal endoscopy: European Society of Gastrointestinal Endoscopy, European Society of Gastroenterology and Endoscopy Nurses and Associates Guideline – Updated June 2015. *Endoscopy* 2015; **47**:1175–1189.
- Riphaus A, Rabofski M, Wehrmann T. Endoscopic sedation and monitoring practice in Germany: results from the first nationwide survey. *Z Gastroenterol* 2010; **48**:392.
- Riphaus A, Geist F, Wehrmann T. Endoscopic sedation and monitoring practice in Germany: re-evaluation from the first nationwide survey 3 years after the implementation of an evidence and consent based national guideline. *Z Gastroenterol* 2013; **51**:1082–1088.
- McQuaid KR, Laine L. A systematic review and meta-analysis of randomized, controlled trials of moderate sedation for routine endoscopic procedures. *Gastrointest Endosc* 2008; **67**:910–923.
- Singh H, Poluha W, Cheung M, et al. Propofol for sedation during colonoscopy. *Cochrane Database Syst Rev* (4):2008;CD006268.
- Riphaus A, Wehrmann T, Hausmann J, et al. Update S3-guideline: 'sedation for gastrointestinal endoscopy' 2014 (AWMF-register-no. 021/014). *Z Gastroenterol* 2016; **54**:58–95.
- Vargo JJ, Delegge MH, Feld AD, et al. Multisociety sedation curriculum for gastrointestinal endoscopy. *Gastrointest Endosc* 2012; **76**:e1–e25.
- Wehrmann T, Grotkamp J, Stergiou N, et al. Electroencephalogram monitoring facilitates sedation with propofol for routine ERCP: a randomized, controlled trial. *Gastrointest Endosc* 2002; **56**:817–824.
- Maeda S, Tomoyasu Y, Higuchi H, et al. Female patients require a higher propofol infusion rate for sedation. *Anesth Prog* 2016; **63**:67–70.
- Haensch K, Schultz A, Krauß T, et al. Women need more propofol than men during EEG-monitored total intravenous anaesthesia. *Biomed Tech* 2009; **54**:76–82.
- Schultz B, Schultz A, Grouven U. Sleeping stage based systems (Narcotrend). In: Bruch HP, Köckerling F, Bouchard R, Schug-Pass C, editors. *New aspects of high technology in medicine*. Bologna: Monduzzi Editore; 2000. pp. 285–291.
- Kugler J. *Elektroenzephalography in Klinik und Praxis*. Stuttgart: Thieme; 1981. pp. 120–146.
- Schultz B, Grouven U, Schultz A. Automatic classification algorithms of EEG-monitor Narcotrend to routinely recorded EEG-data from general anaesthesia: a validation study. *Biomed Eng* 2002; **47**:9–13.
- Schultz A, Grouven U, Schultz B. SEF90; SEF95 and the medication do not discriminate deep EEG stages during propofol/remifentanyl anaesthesia. *Eur J Anaesthesiol* 2000; **17** (Suppl 10):22; (abstract).
- Pilge S, Zanner R, Schneider G, et al. Time delay of index calculation: analysis of cerebral state, bispectral, and narcotrend indices. *Anesthesiology* 2006; **104**:488–494.
- Schneider G, Kochs EF, Horn B, et al. Narcotrend does not adequately detect the transition between awareness and unconsciousness in surgical patients. *Anesthesiology* 2004; **101**:1105–1111.
- Russell IF. The Narcotrend 'depth of anaesthesia' monitor cannot reliably detect consciousness during general anaesthesia: an investigation using the isolated forearm technique. *Br J Anaesth* 2006; **96**:346–352.
- Trampisch HJ, Windeler J. *Medizinische Statistik*. Berlin, Heidelberg: Springer Verlag; 1997.
- Rehm J, Allamani A, Della Vedova R, et al. General practitioners recognizing alcohol dependence: a large cross-sectional study in 6 European countries. *Ann Fam Med* 2015; **13**:28–32.
- Wilhelm W, Buchinger H, Biedler A, et al. Einfluss des Geschlechts auf den Propofolverbrauch und Aufwachzeiten bei standardisierter Anästhesietiefe. *Der Anästhesist* 2005; **54**:567–570.
- Klare P, Hartrampf B, Haller B, et al. Magnetic endoscope imaging for routine colonoscopy: impact on propofol dosage and patient safety – a randomized trial. *Endoscopy* 2016; **48**:916–922.
- Riphaus A, Geist C, Schrader K, et al. Intermittent manually controlled versus continuous infusion of propofol for deep sedation during interventional endoscopy: a prospective randomized trial. *Scand J Gastroenterol* 2012; **47**:1078–1085.
- Ickler G. Patientinnen und Patienten in Krankenhäusern 2012: Diagnosen in Abhängigkeit von Alter und Geschlecht. *Statistische Monatshefte Rheinland-Pfalz* 2014; **06**:527–538.
- Drover DR, Lemmens HJ. Population pharmacodynamics and pharmacokinetics of remifentanyl as a supplement to nitrous oxide anesthesia for elective abdominal surgery. *Anesthesiology* 1998; **89**:869–877.
- Mencke T, Beerhalter U, Fuchs-Buder T. Spontaneous movements, local reactions and pain on injection of rocuronium. A comparison between female and male patients. *Acta Anaesthesiol Scand* 2001; **45**:1002–1005.
- Vuyk J, Oostwouder CJ, Vletter AA, et al. Gender differences in the pharmacokinetics of propofol in elderly patients during and after continuous infusion. *Br J Anaesth* 2001; **86**:183–188.
- Hoymork SC, Raeder J. Why do women wake up earlier than men from propofol anaesthesia? *Br J Anaesth* 2005; **93**:627–633.
- Choong E, Loryan I, Lindquist M, et al. Sex difference in formation of propofol metabolites: a replication study. *Basic Clin Pharmacol Toxicol* 2013; **113**:126–131.
- Loryan I, Lindquist M, Johansson I, et al. Influence of sex on propofol metabolism, a pilot study: implications for propofol anesthesia. *Eur J Clin Pharmacol* 2012; **2**:397–406.
- Sumner AE. The relationship of body fat to metabolic disease: influence of sex and ethnicity. *Gen Med* 2008; **5**:361–371.
- Loryan I, Lindquist M, Johansson I, et al. Influence of sex on propofol metabolism, a pilot study: implications for propofol anesthesia. *Eur J Clin Pharmacol* 2012; **68**:397–406.
- Pleym H, Spigset O, Kharasch ED, et al. Gender differences in drug effects: implications for anesthesiologists. *Acta Anaesthesiol Scand* 2003; **47**:241–259.
- Capri Workshop ESHRE Group. The influence of social factors on gender health. *Hum Reprod* 2016; **31**:1631–1637.