Early Cognitive Impairment After Sedation for Colonoscopy: The Effect of Adding Midazolam and/or Fentanyl to Propofol

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BACKGROUND: The sedative drug combination that produces minimal cognitive impairment and optimal operating conditions during colonoscopy has not been determined. We sought to determine if the use of propofol alone results in less cognitive impairment at discharge than the use of propofol plus midazolam and/or fentanyl in patients presenting for elective outpatient colonoscopy.

METHODS: Two hundred adult patients presenting for elective outpatient colonoscopy were randomized to receive propofol alone or propofol plus midazolam, and/or fentanyl for IV sedation. Baseline cognitive function was measured using the computerized CogState test battery (Cogstate™, Melbourne, Australia) before sedation. During the procedure, sedative drug doses, depth of sedation (via the bispectral index and observer's assessment of alertness/sedation score), complications, and treatability were recorded. Patients were interviewed about recall immediately after emerging from sedation, and cognitive testing was repeated at hospital discharge. Recovery times, quality of recovery, and satisfaction with care were also recorded.

RESULTS: In the propofol plus adjuvants group, 84 patients received fentanyl 50 μg (25–100) (median [range]) and 57 patients received midazolam 2 mg (0.5–10). Patients' cognitive function at discharge was worse than their performance at baseline. However, the changes in cognitive function between discharge and baseline were not significantly different between the two groups. At discharge, 18.5% of patients were cognitively impaired to an extent equivalent to a blood-alcohol concentration of 0.05%. Sedation with propofol plus midazolam and/or fentanyl produced better operating conditions than sedation with propofol alone and was associated with shorter procedure times. Recovery times, recall, dreaming, quality of recovery, and patient satisfaction with care were similar between the groups. Administration of >2 mg of midazolam was a predictor of impaired cognitive function at discharge.

CONCLUSIONS: Significant cognitive impairment was common at discharge from elective outpatient colonoscopy. However, the addition of midazolam and/or fentanyl to propofol sedation did not result in more cognitive impairment than the use of propofol alone. Furthermore, the use of adjuvants improved the ease of colonoscopy without increasing the rate of complications or prolonging early recovery times.

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Colonoscopy is one of the most widely performed procedures worldwide, so effective sedation with prompt recovery is important. Although the goal of sedation is to facilitate the endoscopy, sedation may also result in continuing cognitive impairment that may delay discharge or result in patients being discharged from hospital with levels of cognitive function that contraindicate complex activities of daily living. The drug combination that produces optimal operating conditions although minimizing postoperative cognitive impairment has not been determined.

Propofol alone or combined with midazolam and/or fentanyl is used widely for sedation during endoscopy.[1–3] The risks and benefits of adding adjuvant sedatives or analgesics to propofol are controversial.[4,5] Theoretically, adjuvants may increase patient comfort and improve operating conditions,[4,5] but they

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could also delay return to normal cognition because their duration of action exceeds that of propofol. However, few investigations comparing propofol sedation with or without adjuvants have been conducted and these did not test cognitive function at discharge.[4,6,7]

We therefore tested the hypothesis that, in patients presenting for elective outpatient colonoscopy, the use of propofol alone would result in less cognitive impairment at discharge (as evidenced by an increased reaction time over baseline) than the use of propofol with midazolam and/or fentanyl. In addition, operating conditions, depth of sedation, recovery times, quality of recovery, and satisfaction with care were compared between the two groups.

METHODS

This trial was conducted in the Day Procedure Unit of the Royal Melbourne Hospital between March 2007 and March 2008. All sedation for colonoscopy is administered by anesthesiologists in our institution. Approval by the Human Research Ethics Committee was obtained and each patient gave written informed consent.

Eligible patients were aged ≥18 yr, were of ASA physical status I-III and were presenting for elective colonoscopy. Patients with inadequate English comprehension, mini mental state examination score <26, significant cardio-respiratory instability (ASA IV–V), or prior IV fluid administration were excluded.

All patients received oral bowel preparation the night before endoscopy (two 45-mL doses of sodium phosphate solution [Fleet®, CB Fleet, Australia]). Patients were randomized by computer generation to receive sedation with propofol alone or propofol with adjuvants (midazolam and/or fentanyl). Randomization results were concealed in opaque envelopes until after consent was obtained. Patients, endoscopists, and postoperative observers were blind to group allocation.

Procedure

After consent was obtained, demographic and medical data were recorded and patients completed the CogState brief computerized cognitive test battery.[8,9] On arrival in the endoscopy room, IV access was obtained and oxygen was administered at 4 L/min via a clear plastic mask. Patients were not given IV fluids. Routine patient monitoring included pulse oximetry, electro-cardiography, and noninvasive arterial blood pressure measurement. Bispectral index (BIS) monitoring was also commenced (BIS-XP® Version 4.0, A2000 monitor, 15-s smoothing; Aspect Medical Systems, Newton, MA). The monitor was covered, blinding those present to BIS values during sedation.

Sedative drugs were administered IV according to the randomized group allocation (propofol alone or propofol plus midazolam and/or fentanyl). The method of propofol administration in both groups (i.e., repeated bolus or bolus plus manually controlled infusion) was determined by the anesthesiologist. In the propofol plus midazolam and/or fentanyl group, the choice of one or both drug, and the dosage and administration method for each were determined by the anesthesiologist without further input from the researchers. Adjuvants were administered before propofol. Anesthesiologists were advised to aim for a depth of sedation in which patients were responsive to repeated verbal command (observer's assessment of alertness/sedation [OAA/S] score = 3 [responds only if name called loudly or repeatedly][10]) for the whole procedure. No other instructions were given and the reasons for the choices made by the anesthesiologists were not recorded.

Colonoscopy commenced when the anesthesiologist decided that the depth of sedation was adequate. Predefined complications (over-sedation, undersedation, hypotension, bradycardia, airway obstruction, hypoventilation, hypoxia, nausea and/or vomiting, and pain) were managed according to our study protocol (not shown). Endoscopists were asked to assess patient treatability at the end of endoscopy (the ability to complete the procedure effectively and efficiently) as good, fair, poor, or impossible. After the procedure, patients were transferred to the Stage 1 postanesthesia care unit (PACU) and then subsequently to the Stage 2 PACU from which they were discharged home. The times that patients reached an OAA/S = 5 (assessment every 60 s) and were ready for discharge from the Stage 1 PACU using hospital criteria (oxygen saturation >95% on air, heart rate >55 bpm, systolic blood pressure ±30 mm Hg from preoperative values, orientated, pain score <4/10, no nausea or vomiting) were recorded. Patients were interviewed before Stage 1 PACU discharge using the modified Brice questionnaire.[11] When the patients were classified as ready for hospital discharge (from Stage 2 PACU) according to Chung criteria (score ≥9 of 10),[12] they were questioned about quality of recovery and satisfaction with care and completed the CogState battery a second time.

Measurements

Age, sex, weight, and ASA physical status were recorded, preoperative medications, and quality of recovery score (QoR: a validated 9-point scoring system with a minimum value of 0 and a maximum value of 18[13]) were recorded preoperatively. Oxygen saturation, heart rate, arterial blood pressure, and OAA/S score were recorded every 2.5 min during sedation. BIS data were downloaded from the monitor with patient consent using software provided by Aspect Medical Systems. Recordings with signal quality below 50 were removed from the analysis. Sedation time was defined as the time from administration of the first drug and until removal of the endoscope. Endoscopy time was defined as time from the insertion of

the endoscope and until removal of the endoscope. Recovery times, including the time to OAA/S = 5, time to Stage 1 PACU discharge, time to commencement of the discharge cognitive testing, and time to hospital (Stage 2 PACU) discharge, commenced at the removal of the endoscope. Patient satisfaction with anesthetic care was measured using a 100-mm visual analog scale (0 = completely dissatisfied and 100 = completely satisfied).

Cognitive Testing

The CogState brief computerized test battery (Cogstate™, Melbourne, Australia) consisted of four tests and these are summarized in Table 4. The tests measured psychomotor function (Detection task: "Has the card turned over?"), attention (Identification task: "Is the card red?"), visual memory (One Card Learning task: "Have you seen this card before in this task?"), and working memory (One Back task: "Is the card the same as the previous card?") and required approximately 10 min for completion. These tasks have been described in detail previously[8,9,14–16] and were administered according to standard instructions.

Statistical Analyses

For each CogState task nonnormally distributed data were log-transformed before calculating mean reaction times and accuracy.[14,15] The primary end point for this study was the difference in performance on the CogState Detection task between the discharge and baseline assessments. Secondary end points included OAA/S scores, BIS, complications, treatability, recovery times, dreaming, QOR scores, and patient satisfaction with sedation.

The sample size was calculated from the results of a pilot study of 70 patients who received sedation with propofol and adjuvants. Reaction time on the Detection task increased from 2.58 $\log_{10}$ ms (standard deviation: 0.08 ms) at baseline to 2.77 $\log_{10}$ ms (SD = 0.09) ms after sedation (7.3% increase). We assumed that sedation with propofol alone would result in a smaller increase in reaction time on the Detection task (approximately 25%) than would sedation with propofol and adjuvants (i.e., a detection task speed post sedation = 2.72 $\log_{10}$ ms). Therefore, 76 patients per group were required ($\alpha = 0.05$ [two-tailed]; $\beta = 0.2$). Two hundred patients were studied to allow for any loss to follow-up.

Continuous data were tested for normality. Normally distributed data were summarized using mean and standard deviation and were compared using unpaired two-tailed *t*-tests. Skewed data were summarized using median and range and were compared using Wilcoxon's ranked sum test. Categorical data were summarized using number (%) and were compared using χ^2 test or Fisher's exact test. Paired data were compared using paired two-tailed *t*-tests or signed-rank tests. When there were more than two groups, normally distributed data were compared using analysis of variance and skewed data were compared using the Kruskell–Wallis test. Measures of effect size were used to express the magnitude of differences between- (Cohen's d) or within-groups (Dunlaps' d).[8,16]

Change in cognitive function was also analyzed at the level of individual patients. To achieve this, a reliable change index was used to express change from baseline to discharge in the speed of performance on the Detection task for each patient (i.e., speed of performance at discharge minus speed of performance at baseline divided by the group within subject standard deviation[14]). Previous studies have shown that a 0.05% breath alcohol concentration is associated with a decline in performance of one standard deviation on this task,[9] and therefore patients with an reliable change index of one or more were classified as having undergone clinically significant cognitive change.

Logistic regression was used to determine predictors of impaired cognitive function, treatability, and dreaming. Categorical variables were created from continuous variables where applicable. Predictors from univariate analyses with *P* values <0.2 were included in the multivariate models. Stepwise elimination of predictors were used to arrive at a parsimonious model and tested for interactions. Analysis of the randomized comparison (propofol alone versus propofol plus adjuvants) was conducted on an intention-to-treat basis. All analyses were conducted using Stata 9.0. A $P < 0.05$ was considered statistically significant.

RESULTS

The trial profile is outlined in Figure 1. Patients who received drugs other than propofol, midazolam, and fentanyl were replaced. Five patients with protocol violations involving midazolam and fentanyl were analyzed in their randomized groups on an intention-to-treat basis. Ninety-seven patients in the propofol only group and 98 patients in the propofol plus adjuvants group completed the discharge cognitive test and were eligible for inclusion in the analysis of the primary outcome.

Patients were similar at baseline except that more patients in the propofol alone group were taking selective serotonin reuptake inhibitors (SSRIs) than in the propofol plus adjuvants group (Table 1). Because of this apparent inequality, we tested this difference for significance ($P = 0.022$).[17] In the propofol plus adjuvants group, 84 patients received fentanyl 50 μg (25–100) (median [range]) and 57 patients received midazolam 2 mg (0.5–10). Eight-three percent of patients in each group were administered propofol by repeated bolus and 17% were administered propofol bolus plus manually controlled infusion ($P = 1.0$). Propofol doses were substantially higher in the propofol alone group than in the propofol plus adjuvants

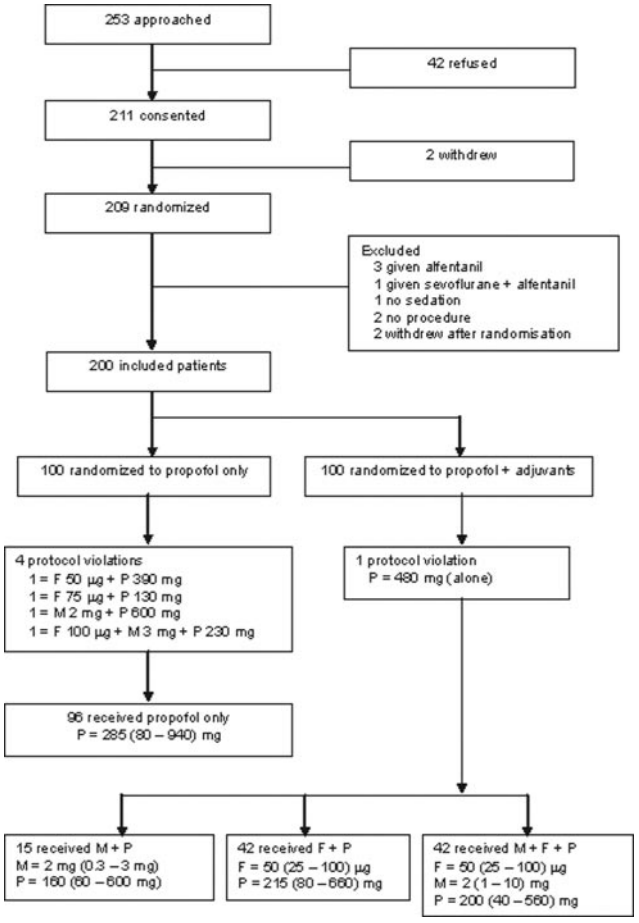

Figure 1. Flow chart of patients. P = propofol; M = midazolam; F = fentanyl.

Table 1. Baseline Data

	Propofol + adjuvants (n = 100)	Propofol alone (n = 100)
Age (yr)	48 ± 16	51 ± 14
Sex (M)	47 (47)	46 (46)
Weight (kg)	78 ± 17	79 ± 20
ASA physical status		
I	37 (37)	35 (35)
II	47 (47)	51 (51)
III	16 (16)	14 (14)
Preoperative SSRIs	4 (4)	13 (13)*
Other preoperative antidepressants or antipsychotics	5 (5)	5 (5)
Preoperative opioids	3 (3)	3 (3)
Preoperative QoR score	15 (10–18)	15 (7–18)

Data presented as mean ± SD (normally distributed data), median (range) (skewed data), or number (%) (categorical data).

ASA = American Society of Anesthesiologists; SSRI = selective serotonin receptor antagonist; QoR = quality of recovery score.

* Because of this apparent inequality, we tested this difference for significance (P = 0.022).

group, but OAA/S scores and BIS values were not significantly different (Table 2). Minimum systolic blood pressures, heart rates, respiratory rates, and oxygen saturations were acceptable and rates of complications were low. There were no clinical differences between the two groups (results not shown).

Treatability was rated as "fair" in 20% of propofol alone patients compared with 10% propofol plus adjuvants patients (P = 0.048). Endoscopy times were significantly longer in the propofol alone group compared with the propofol plus adjuvants group (22 vs 17 min; P = 0.01).

In the multivariate model, predictors of "good" treatability were lower ASA physical status and the administration of midazolam (Table 3). Recovery times, incidences of dreaming and recall, and QOR scores were similar in the two randomized groups. Patients who received midazolam took longer to reach an OAA/S = 5 after the procedure than patients who did not (10 vs 7 min; P = 0.041). Times to Stage 1 PACU discharge (22 vs 21 min; P = 0.9188) and hospital discharge (64 vs 65 min; P = 0.4603) were similar.

Completion rates for patients attempting the CogState tasks were high (Detection task = 97.4%, Identification task = 98.5%, One Card Learning task 98.5%, and One Back task = 98.9%). When considered for the entire sample, performance at discharge had declined significantly from baseline for the Detection (P = 0.0024) and Identification (P = 0.0001) tasks, but not for the One Card Learning or One Back tasks (Table 4). However, the magnitude of decline in cognitive function was small for both tasks (Table 4) and not significantly different between the two randomized sedation groups (Table 5). When considered for individual patients, 37 patients (18.5%) were classified as showing clinically significant cognitive decline. Multivariate analysis indicated that the predictors of this decline were the consumption of psychotropic drugs preoperatively and administration of more than 2 mg of midazolam during the procedure (Table 6).

DISCUSSION

Sedation for endoscopy should provide optimal operating conditions although allowing rapid recovery so that the patients can return to their normal lives safely and promptly. Drug selection is a crucial determinant of these outcomes. Contrary to our initial hypothesis, the use of propofol alone did not result in less cognitive impairment at discharge than the use of propofol plus adjuvants. Nor did propofol alone confer any benefit in terms of complications, QOR scores, or time to hospital discharge. In fact, the use of propofol alone was associated with poorer treatability and longer endoscopy times.

Among the studies researching drug combinations for endoscopy, only three have made similar comparisons to ours.[4,6,7] Seifert et al.[6] reported faster hospital discharge times in propofol alone patients than in propofol plus midazolam patients having gastroscopy, but they prescribed fixed doses of midazolam (2.5 mg [<70 kg] or 3.5 mg [≥70 kg]). Fanti et al.[7] found no difference in hospital discharge times between propofol alone and propofol plus midazolam

Table 2. Intraoperative and Postoperative Data

	Propofol + adjuvants (n = 100)	Propofol alone (n = 100)	P
Induction time (min)	2 (0–7) [1–3]	2 (0–20) [1–3]	0.0457
Scope time (min)	17 (1–76) [13–24]	22 (2–86) [13–30]	0.0151
Sedation time (min)	20 (3–67) [14–27]	25 (5–87) [16–33]	0.0051
Propofol (mg)	200 (40–660) [120–280]	285 (80–940) [200–410]	<0.0001
OAA/S			
Minimum	1 (0–5) [1–2]	1 (0–4) [1–2]	0.2278
Median	2 (0–5) [2–3]	2 (0–5) [2–3]	0.06
Maximum	4 (0–5) [3–5]	4 (0–5) [3–4]	0.1969
Bispectral index			
Minimum	47 (23–82) [37–58]	42 (17–79) [36–49]	0.0677
Median	63 (30–90) [57–71]	60 (33–92) [51–69]	0.1574
Minimum	78 (44–97) [72–86]	77 (43–98) [72–84]	0.4533
Treatability			
Impossible	0 (0)	0 (0)	0.048
Poor	0 (0)	0 (0)	
Fair	10 (10)	20 (20)	
Good	90 (90)	80 (80)	
Time to OAA/S = 5 (min)	9 (0–60) [5–14]	7 (0–63) [4–14]	0.1440
Time to PACU discharge (min)	21 (0–60) [16–29]	21 (5–83) [15–30]	0.8516
Time to CogState test (min)	51 (34–107) [44–60]	52 (26–143) [44–63]	0.8599
Time to hospital discharge (min)	64 (19–177) [52–71]	66 (32–147) [54–78]	0.2046
Recall	3 (3)	4 (3)	1.0
Dreaming	16 (16)	22 (22)	0.279
Discharge QoR score	17 (9–18) [16–18]	17 (8–18) [15–18]	0.6601
QoR difference score	1 (−4 to 7) [0–2]	1 (−5 to 8) [0–2]	0.9437
Patient satisfaction			
Dissatisfied	0 (0)	1 (1)	0.721
Neutral	3 (3)	4 (4)	
Satisfied	97 (97)	95 (95)	

Data presented as mean ± SD (normally distributed data), median (range) [interquartile range] (skewed data), or number (%) (categorical data).

OAA/S = observer's assessment of alertness/sedation score[15]; SBP = systolic blood pressure; PACU = postanesthesia care unit; Induction time = time from start of drug administration to insertion of endoscope; Endoscope time = time from endoscope insertion to endoscope removal; Sedation time = time for start of drug administration to endoscope removal; Times to OAA/S = 5, PACU discharge, discharge CogState test, and hospital discharge start at the time of endoscope removal; QoR = quality of recovery.[18]

Table 3. Predictors of Good Patient Treatability

Characteristic	n (%)	Univariate OR (95% CI)	P	Adjusted OR (95% CI)	P
Group[a]					
Propofol plus adjuvants	90 (90)	1.00			
Propofol alone	80 (80)	0.44 (0.20–1.00)	0.052		
Age (yr)					
<50	87 (86)	1.00			
≥50	83 (84)	0.83 (0.38–1.82)	0.649		
Sex					
Male	80 (86)	1.00			
Female	90 (84)	0.86 (0.39–1.88)	0.706		
Weight (kg)					
<100	149 (87)	1.00			
≥100	21 (75)	0.46 (0.18–1.21)	0.117		
ASA physical status					
I	66 (92)	1.00		1.00	
II–III	104 (81)	0.39 (0.15–1.01)	0.054	0.38 (0.14–0.98)	0.045
SSRI, other psychotropic or opioid					
No	147 (87)				
Yes	23 (72)	0.36 (0.149–0.89)	0.028		
Midazolam administered[b]					
No	115 (82)	1.00		1.00	
Yes	55 (93)	3.11 (1.03–9.34)	0.043	3.25 (1.07–9.85)	0.037
Fentanyl administered[b]					
No	91 (81)				
Yes	79 (91)	2.39 (1.01–5.66)	0.048		

OR = odds ratio; 95% CI = 95% confidence interval; ASA = American Society of Anesthesiologists; SSRI = selective serotonin reuptake inhibitor.

[a] As randomized (intention-to-treat).

[b] As administered. In the propofol plus adjuvants group, anesthesiologists were asked to administer one or either drug according to their preference. In the propofol alone group, two patients received propofol and three received midazolam (protocol violations).

Table 4. Cognitive Function at Baseline and Discharge

Task	Outcome measure	Before	After	*P*	Effect size
Detection (log_{10} ms) ($n = 190$)	Speed of performance	2.53 ± 0.11	2.55 ± 0.11	0.0024	−0.15
Identification (log_{10} ms) ($n = 192$)	Speed of performance	2.72 ± 0.08	2.74 ± 0.08	<0.0001	−0.32
One-card learning (arcsine accuracy) ($n = 192$)	Accuracy of performance	0.77 ± 0.16	0.75 ± 0.17	0.0971	0.13
One-back memory (arcsine accuracy) ($n = 187$)	Accuracy of performance	1.16 ± 0.27	1.15 ± 0.32	0.8022	0.02

An increase in reaction time (detection and identification) and a decrease in accuracy (one-card learning and one-back memory) indicate impairment.

Effect size = difference between means/Dunlap's d.

Table 5. Change in Cognitive Function from Baseline

Task	Total	Propofol + adjuvants	Propofol alone	*P*	Cohen's d
Detection (log_{10} ms)	($n = 190$) 0.02 ± 0.08 (−0.22 to 0.26)	($n = 96$) 0.02 ± 0.08 (−0.22 to 0.26)	($n = 94$) 0.01 ± 0.07 (−0.18 to 0.21)	0.6133	0.133
Identification (log10 ms)	($n = 192$) 0.02 ± 0.06 (−0.2 to 0.22)	($n = 97$) 0.03 ± 0.06 (−0.13 to 0.22)	($n = 95$) 0.02 ± 0.06 (−0.2 to 0.17)	0.0618	0.167
One-card learning (arcsine accuracy)	($n = 192$) −0.02 ± 0.18 (−0.55 to 0.42)	($n = 96$) −0.03 ± 0.19 (−0.55 to 0.41)	($n = 96$) −0.01 ± 0.17 (−0.55 to 0.42)	0.5797	−0.055
One-back memory (arcsine accuracy)	($n = 187$) −0.005 ± 0.26 (−1.04 to 0.65)	($n = 95$) −0.03 ± 0.28 (−1.04 to 0.65)	($n = 92$) 0.19 ± 0.24 (−0.71 to 0.53)	0.2142	−0.843

An increase in reaction time (detection and identification) and a decrease in accuracy (one-card learning and one-back memory) indicate impairment.

Cohen's d (effect size) = difference between means/pooled standard deviation.

patients having upper gastrointestinal ultrasound, but they prescribed a relatively low midazolam dose (20 μg/kg). Finally, VanNatta and Rex[4] compared propofol alone with propofol plus midazolam (1 mg), propofol plus fentanyl (25 μg), and propofol plus midazolam (1 mg) and fentanyl (25 μg) in patients having colonoscopy. Combination therapy led to faster discharge times, but the propofol alone group was deliberately titrated to a deeper level of sedation than the other groups. Because of this design issue and others, such as fixed dosing and absence of cognitive testing, these studies cannot be compared directly to ours. Furthermore, as was evident in this study, cognitive function may still be abnormal when discharge criteria are met.

Other studies have investigated cognitive impairment after colonoscopy. Theodorou et al.[18] demonstrated impaired performance up to 120 min after propofol/midazolam/fentanyl or nitrous oxide/sevoflurane sedation for colonoscopy. In contrast, Moerman et al.[19] found no cognitive impairment after 15 min in colonoscopy patients sedated with propofol or remifentanil. However, neither study identified the number of patients who were significantly impaired at discharge nor the predictors of impaired performance.

The only modifiable factor we identified that predicted cognitive impairment in individuals at discharge was administration of >2 mg of midazolam, whereas fentanyl use was not a predictor of cognitive impairment. In patients having general anesthesia for laparoscopic sterilization, Richardson et al.[20] demonstrated that patients who received midazolam (40 μg/kg) were cognitively impaired up to 30 min postoperatively, whereas those who received placebo were not. In volunteers receiving propofol, fentanyl, and midazolam, Thapar et al.[21,22] identified midazolam as the key drug producing prolonged psychomotor impairment (equivalent to a blood alcohol of 0.11%). In contrast, Fredman et al.[23] reported that midazolam (0.5 or 2 mg given 30 min preinduction) had no effect on psychomotor tests, but prolonged Stage 1 PACU discharge time in patients having minor urological surgery. This highlights the poor correlation of cognitive function tests and discharge criteria and the need for greater clarity about the predictors of cognitive impairment at discharge.[23]

Colonoscopy was more difficult in patients in the propofol alone group. BIS values, OAA/S scores, sedation-related complications, early recovery times, and recall were similar in the two groups and were consistent with those recorded in other studies of procedural sedation using propofol-based techniques.[24,25] Perhaps deeper sedation is required if propofol is used alone or the quality of propofol alone sedation is not particularly suited to colonoscopy.

The only modifiable factor we identified that predicted "good" treatability was the administration of midazolam. As depth of sedation was not a predictor of treatability, the reason for this finding is obscure. Midazolam has central muscle relaxant properties,[26] but to suggest this as a mechanism is purely speculative. Previous studies have reported no differences in patient cooperation as rated by the endoscopist between patients who received midazolam and those who did not.[6,7]

Table 6. Predictors of Postsedation Impairment on Detection Task

Predictor	*n* (%)	Univariate OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
Age (yr)					
<50	22 (22)	1.00			
≥50	15 (16)	0.67 (0.32–1.39)	0.287		
Sex					
Male	16 (19)	1.00			
Female	21 (20)	1.11 (0.54–2.28)	0.783		
ASA physical status					
I	16 (22)	1.00			
II–III	21 (18)	0.76 (0.36–1.57)	0.456		
Preoperative SSRIs					
No	34 (20)	1.00			
Yes	3 (18)	0.88 (0.23–3.22)	0.842		
Other preoperative psychotropic drugs					
No	32 (18)	1.00			
Yes	5 (50)	4.62 (1.26–16.92)	0.021	5.38 (1.46–19.92)	0.012
Preoperative opioid drugs					
No	34 (18)	1.00			
Yes	3 (60)	6.66 (1.07–41.42)	0.042		
Fentanyl dose					
≤50 μg	29 (19)	1.00			
>50 μg	8 (20)	1.08 (0.45–0.61)	0.854		
Midazolam dose					
≤2 mg	31 (18)	1.00			
>2 mg	6 (43)	3.51 (1.14–10.83)	0.029	4.04 (1.29–12.60)	0.016
Mean OAA/S during sedation					
≤2	20 (19)	1.00			
>2	17 (20)	1.12 (0.54–2.30)	0.757		
General anesthesia					
No	25 (17)	1.00			
Yes	12 (26)	1.68 (0.74–3.69)	0.196		
Sedation time (min)					
≤21	19 (18)	1.00			
>21	18 (20)	1.09 (0.53–2.24)	0.806		
Discharge test (min)					
≤62	27 (19)	1.00			
>62	10 (22)	1.25 (0.55–2.83)	0.595		

OR = odds ratio; 95% CI = 95% confidence interval; ASA = American Society of Anesthesiologists; SSRI = selective serotonin reuptake inhibitor; OAA/S = observer's assessment of alertness/sedation score[15]; General anesthesia (90% of sedation time with bispectral index <60); Sedation time = time for start of drug administration to endoscope removal; Discharge test = time from endoscope removal to time of discharge Cogstate™ test.

This study has several limitations. The trial was not designed to assess the effects of fentanyl and midazolam separately; our interest was in determining if the use of any adjuvants to propofol impaired cognitive function at discharge. The fact that the choice of adjuvants was not random limits our ability to draw conclusions about their individual effects because of the potential for confounding, but raises hypotheses and provides pilot data for testing in the future. Rather than using fixed doses, we targeted the same depth of sedation by individually titrating doses in each patient and used BIS monitoring as a measure of drug effect.[27] This raises the issue that a different depth of sedation may be required for good conditions with different sedative combinations. In addition, more patients in the propofol alone group were taking SSRIs than patients in the propofol plus adjuvants group. For this reason, we included SSRIs as a variable in multivariate models predicting impaired cognitive function (SSRIs were not a significant predictor). A further potential limitation is the possibility of a practice effect obscuring postsedation impairment, given the brief test-retest interval and use of only one practice session. However, this approach is supported by studies in young and older patients studied repeatedly at short intervals[15,28] and is practical in the setting of ambulatory surgery. In both studies, improvements between assessments were most marked between the first and second assessment, with performance remaining fairly stable between subsequent assessments. Other factors also may have influenced our patients' performance on the test battery at baseline and/or discharge, such as fatigue, hunger, thirst, anxiety, and depression. Although these factors may have operated randomly, they should have acted equally for the two randomized groups. Finally, cognitive function could have been measured at a set time rather than before each patient was deemed ready for discharge. Although both approaches may lead to variability in the extent of recovery at testing, our hypothesis related to cognitive function when patients left hospital.

In conclusion, significant cognitive impairment was common at discharge after elective outpatient colonoscopy. However, the addition of midazolam and/or fentanyl to propofol sedation did not result in more

cognitive impairment than the use of propofol alone. Furthermore, the use of adjuvants improved the ease of colonoscopy without increasing the rate of complications or prolonging early recovery times. The only modifiable factor predicting cognitive impairment in individuals at discharge was administration of >2 mg of midazolam.

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