Original Article

Recovery of cognitive function after sedation with propofol for outpatient gastrointestinal endoscopy

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Abstract

Background/Aim: Most endoscopies performed in the United States utilize sedation. Anesthesia provides patient comfort and improved procedural quality but adds to the complexity of scheduling routine outpatient procedures. We aimed to assess the return of cognitive function after propofol administration in patients undergoing outpatient endoscopies.

Patients and Methods: Cognitive recovery for patients undergoing endoscopy under monitored anesthesia care was evaluated using EncephalApp. Patients were tested before and after procedure and healthy controls were tested twice, 30 min apart. Results were tabulated in on state (on time) and off state (off time) and total time (on time + off time). The time difference between pre- and post-tests, "delta," was calculated for on, off, and total times. Wilcoxon rank test was used to check the difference in mean delta of all three test times between cases and controls and to check for statistical significance.

Results: The difference in mean time between cases and controls was significant for off ($P < 0.0001$) and total ($P = 0.0002$) times. No statistically significant difference was noted in mean time for on time ($P = 0.013$) between cases and controls. Cognitive flexibility, a measure of on time, returned to baseline after procedural sedation even though psychomotor speed, a measure of off time and total time, had not.

Conclusion: Cognitive flexibility returns to baseline within 30–45 min after propofol sedation despite delayed return of psychomotor speed and reaction time.

Keywords: Cognitive recovery, EncephalApp, endoscopy, propofol, sedation

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INTRODUCTION

Gastrointestinal (GI) endoscopies performed in the United States (US) have almost quadrupled over the past few decades,[1] with roughly 19 million procedures performed in 2009 alone.[2] Procedures performed without the aid of sedation have little acceptance in the US, and most endoscopists rely on sedation for routine and advanced procedures.[3] The benefits of moderate sedation, formerly called conscious sedation, include adequate pain and anxiety control and amnesia[4] while allowing patients to maintain their airway and breathe spontaneously, spurred by verbal cues.[5] In the US, some form of sedation is utilized for safe completion of nearly all of colonoscopies and esophagogastroduodenoscopies (EGDs).[6,7]

Standard sedation, the combination of a benzodiazepine and an opioid, is the most commonly used form of sedation for endoscopy.[8] The introduction of propofol was associated with shorter induction and recovery periods,[9]

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improved sedation and amnesia, improved patient cooperation, and comparable patient satisfaction, without any increase in cardiopulmonary complications.[9,10,11] Rapid recovery from propofol impacted practice efficiency and offered economic advantages when compared to standard sedation.[12] Moreover, propofol was safe for sedation in patients with cirrhosis,[13] without exacerbating covert hepatic encephalopathy (HE)[14] when compared to midazolam.[15] In children, propofol, when combined with fentanyl or midazolam, provided more effective sedation and ease of endoscopy than propofol alone[16] without increasing cognitive impairment, complications, or recovery period.[17] Moreover, when combined with fentanyl or midazolam, utilization of smaller doses of propofol led to shorter recovery times and comparable patient satisfaction compared to propofol titrated to deep sedation.[18,19]

Despite multiple studies validating propofol, and its association with faster and improved postprocedure recovery, anesthesia guidelines continue to recommend that patients do not drive or use public transportation without escort for 24 h.[20] This recommendation can generate additional hardship for patients as they require participation from a family member or neighbor for transportation after their procedure. As a result, multiple schedules need to be coordinated in an attempt to arrange procedures, thus increasing the rate of cancellations. We set out to study the recovery in cognitive function after propofol sedation for outpatient endoscopy. Historically, other methods of evaluating recovery after sedation, including Digit Symbol Test,[21] Stroop Color and Word Test,[21] Trail Making Test,[21] Cogstate computerized test battery,[17] and driving simulator test,[20] have been performed. In an attempt to streamline the process of comparing pre- and postprocedure cognitive function, we utilized a smartphone-based app. To our knowledge, this is the first report of utilizing this method in this area of research.

PATIENTS AND METHODS

Developed to diagnose covert HE, EncephalApp, a smartphone-based Stroop app, was used to test all patients with cirrhosis.[22] Available on the iTunes store, the app was uniformly administered to all subjects on the same device, an iPhone 6. This app has the advantages of having self-explanatory instructions, not requiring bulky equipment, being easy to use (even for people unfamiliar with a smartphone), having minimal potential for human error (the app generates its own data),[23] and does not require any expertise to interpret results.

EncephalApp has two components, depending on the presence of congruent and incongruent stimuli, an "off state" and an "on state." Each state is compiled of five separate runs of tests preceded by two practice runs, administered in succession, without a break.

In the easier off state, the subject sees sequential, neutral stimuli in the form of pound or hash signs () presented in red, blue, or green. Responding as quickly as possible, subjects touch the name of the color displayed at the bottom of the phone screen corresponding to the color of pound or hash signs. The names of colors displayed on the bottom of the screen are not fixed and change for each presentation. Once 10 presentations are answered correctly, the run is completed. An error in matching stops the run and the subject has to retake that individual run. The subject has to complete five runs accurately to complete the off state. The time taken to complete the five runs in the off state is called the "off time."

In the more difficult on state, discordant stimuli are presented. The subject is expected to touch the color of the word presented, not the color it reads. For example, when the word "GREEN" is presented in blue colored letters, the correct answer is "blue," not "green." Additionally, the on state is also timed. Similar to the off state, five runs need to be completed successfully to finish the on state. The time taken to complete the five runs in the on state is called the "on time." The sum of off time and on time is called "total time." EncephalApp consists of four practice runs and 10 separate runs of tests[23] with half of them being off state and half of them being on state and takes 5–10 min to complete.

Cases were tested once before and once 30–45 min after procedure and controls were tested twice, 30 min apart. The tests were called pre-test for the first round and posttest for the second round for both cases and controls. The results of off time, on time, and total time (off time + on time) were calculated for both cases and controls, and for both pre- and post-tests, and were compared.

We used the following terms as part of the study and the explanations are below. The terminology applies to both cases and controls:

1. Off time: Time taken to complete the off state – called "pre-off time" for the first round and "post-off time" for the second round
2. On time: Time taken to complete the on state – called "pre-on time" for the first round and "post-on time" for the second round
3. Total time: Time taken to complete both off and on states – called "pre-total time" for the first round and "post-total time" for the second round

4. Delta: The difference between pre- and post-times (post-time minus pretime)
    a. "Delta off time" is post-off time minus pre-off time
    b. "Delta on time" is post-on time minus pre-on time
    c. "Delta total time" is post-total time minus pre-total time.

Patients who presented to the outpatient endoscopy suite at West Virginia University Hospitals (WVUH) for EGD, colonoscopy, EGD and colonoscopy, or endoscopic ultrasound (EUS) were randomly recruited to the study. Patients undergoing endoscopic retrograde cholangiopancreatography were excluded as our center utilizes general anesthesia for these procedures. All patients were agreeable to sedation with propofol for their respective procedures. After institutional review board approval, we randomly recruited 119 patients scheduled to undergo outpatient endoscopy (cases) on a first-come-first-serve basis. Of the 119 patients recruited, 50 patients had EGDs, 51 had colonoscopies, 15 had combined EGD and colonoscopies, and 3 had EUSs.

Additionally, 50 healthy controls (controls) were randomly recruited to the study from waiting areas at the WVUH. Written informed consent was obtained from all subjects. All subjects, cases and controls, were screened to confirm that they were 18 years of age or older, did not have cirrhosis, a history of stroke, or dementia, and had not started any psychiatric medications or narcotics or used illicit drugs in the 4-week period prior to testing.

Data were collected in the form of off time, on time, and total time for both cases and controls and delta was calculated for off, on, and total times. The delta for cases and delta for controls were compared to determine if the delta was equivalent between the groups or if there was a statistically significant difference between them.

Propofol was the principal sedative used for all cases. Additional agents such as lidocaine, dexmedetomidine, midazolam, or ketamine were used, and on occasion, one or more of these four agents were used in combination with propofol depending on provider preference.

Statistical analysis

The primary outcome variables in this study include the timing data between the pre- and post-test. Descriptive statistics and exploratory data analysis were performed first to summarize the baseline data. Categorical data were described using contingency tables. Continuously scaled measures were summarized with descriptive statistical measures [i.e., mean (±SD) and median (range)]. Chi-square test and Wilcoxon rank test were applied to assess the balance of categorical variables and continuous variables between patients and controls. For the data analysis on the outcome variables, Wilcoxon signed rank test for paired data was used to assess the difference in timing between the pre- and post-test, whereas Wilcoxon rank test was used to compare the outcome variables between patients and controls. All statistical tests where two-sided $P < 0.05$ were considered statistically significant.

RESULTS

Baseline characteristics for cases and controls were similar in multiple aspects [Table 1]. Differences in gender, ethnicity, education, and age were not statistically significant across the groups, although the controls were approximately 4 years younger than cases.

The calculated mean total pretest time was 160 s and mean total post-test time was 164 s for cases. For controls, the mean total pre-test time was 147 s and the mean total post-test time was 143 s [Table 2]. When investigated further, dividing total time into off time and on time, the results showed a similar pattern. For the cases, the pre-off and post-off times were 72 and 77 s, respectively, and the pre-on and post-on times were 88 and 87 s, respectively. For the controls, the pre-off and post-off times were 67 and 66 s, respectively, and the pre-on and post-on times were 80 and 76 s, respectively. The on times were consistently longer than off times due to the complexity of the on state as it involves discordant stimuli. Comparing cases and controls, head to head, would show the differences between the groups but the aim of the study is to determine the difference in test results before and after testing to see if sedation had any effect on cognition. Hence, delta was

Table 1: Demographics

	Cases (*n*=119)	Controls (*n*=50)	*P*
Sex			0.86
Male (%)	46 (38.7)	18 (36.0)	
Female (%)	73 (61.3)	32 (64.0)	
Ethnicity			0.99
Caucasian (%)	118 (99.2)	50 (100)	
Asian (%)	1 (0.8)	0 (0)	
Age	50.76±14.06	46.66±16.95	0.14
Years of education	15.5±2.97	15±2.52	0.26

Table 2: Mean of time

Mean of test time in cases and controls: Pre, post, and total						
	Pre-off time	Post-off time	Pre-on time	Post-on time	Pre-total	Post-total
Cases	72.90	77.50	88.02	87.06	160.92	164.56
Controls	67.64	66.63	80.18	76.40	147.82	143.0
P-value	0.14	<0.0001	0.13	0.005	0.12	0.001

calculated to contrast the time taken to complete the testing before and after sedation for endoscopy.

Delta (post-test time minus pre-test time) and mean of delta were calculated for off time, on time, and total time for both cases and controls to determine the difference in time taken to complete the test before and after endoscopy. These results (both cases and controls) were compared to determine if there were any differences [Table 3]. Mean delta for cases was 4.5, –0.9 and 3.64 s for off, on, and total times, respectively. Mean delta for controls was –1, –3.7 and –4.7 s for off, on, and total times, respectively. The results are listed in Table 3.

Wilcoxon signed rank test for paired data was used to assess pre- and post-data for each group separately – cases and controls [Table 2]. Wilcoxon signed rank test was used to assess the difference in mean delta of off time, on time, and total time between cases and controls [Table 3] and the results are as below:

- For mean delta of off time, controls ($P = 0.071$) were 6 s quicker in the post-test than in the pre-test when compared to cases ($P < 0.0001$)
- For mean delta of on time, controls ($P = 0.001$) were about 5 s quicker in the post-test than in the pre-test when compared to cases ($P = 0.41$)
- For mean delta of total time, controls ($P = 0.006$) were about 7 s quicker in the post-test than in pre-test when compared to cases ($P = 0.013$).

We hypothesized that if the delta of times of cases for off time, on time, and total time were comparable to delta of times of controls for off time, on time, and total time, it could be safely inferred that propofol sedation did not compromise cognitive function. This would require determining if there is a statistically significant difference in delta between cases and controls.

When statistical significance of mean delta scores was calculated using the above data, the following results were obtained [Table 4]:

- The difference in mean delta of off time between cases and controls is statistically significant ($P < 0.0001$)
- The difference in mean delta of on time between cases and controls is not statistically significant ($P = 0.013$)
- The difference in mean delta of total time between cases and controls is statistically significant ($P = 0.0002$).

The above results showed off time and total time to be compromised in cases when compared to controls, but on time was not compromised as the difference in delta did not achieve statistical significance.

Table 3: Mean of delta (post-test time minus pre-test time, based on Wilcoxon sign rank test for paired data)

Type	Mean	Std. deviation	*P*
Off time of cases	4.5976	8.9607	<0.0001
On time of cases	−0.9566	10.7589	0.41
Total time of cases	3.6409	17.2987	0.013
Off time of controls	−1.0144	8.7518	0.071
On time of controls	−3.7834	8.2791	0.001
Total time of controls	−4.7979	12.8052	0.006

Table 4: Significance of the difference of mean delta between cases and controls

	P-values of two-sample test of mean of delta		
Type	Mean delta of total time	Mean delta of off time	Mean delta of on time
P-value	0.0002	<0.0001	0.013

DISCUSSION

Cognitive recovery after endoscopic sedation has been studied with renewed interest with the widespread use of propofol. In addition to increased patient satisfaction, sedation with propofol provides a quicker recovery period[9] without more complications compared to standard sedation. Keeping in line with increasing operational efficiency, any pre-, intra-, or postprocedural improvement should impact patient care and safety and quality outcomes. Safely discharging patients remains a priority, yet, there are several barriers to this process. Availability, or lack thereof, of escort can have an impact on patient's compliance with endoscopy. When unable to follow current recommendations, patients that lack an escort result in absenteeism for endoscopy with subsequent treatment delays and financial losses.[24] Endoscopy units have always sought for ways to improve compliance, thus improving institutional efficiency. Our goal was to evaluate the safe discharge of patients, on their own recognizance, thus reducing reliance on a second adult, which complicates the scheduling process.

The need for an escort could be a deterrent for compliance with outpatient endoscopy, based on prior studies. It has been shown that patients who live more than 20 miles away had a higher chance of not showing up, when compared to those who lived 5–20 miles from the hospital. They also noted that patients who had less than or equal to three people in the household had a higher chance of not showing up when compared to those who had four or more people in the household.[25] Married patients were more likely to show up for their procedures suggesting a potentially higher likelihood of escort availability for married patients.[24] These factors can be loosely linked to a need for escort for patients presenting for endoscopy and the need for the escort to be tied up, while the

patient has the procedure. This could be one of the main hindrances for such patients to show up, thereby decreasing compliance and deny vital services. If patients undergoing endoscopy could be allowed to go home after cognitive recovery without escort, it has the potential to dramatically decrease absenteeism for endoscopy.

Utilizing EncephalApp, we aimed to quantify the return of cognition to baseline within 30–45 min after completion of an endoscopic procedure when propofol was used for sedation, either alone or in conjunction with other sedatives. We chose this time as this is the average time after a procedure when the patient is discharged home. As described above, the app actively engages the user by presenting stimuli that require thought and motor response to successfully complete a timed task, thus measuring cognition.[23] The off state is a measure of psychomotor speed and reaction time. However, due to the use of discordant stimuli, the demand for cognitive processing is higher during the on state as it involves psychomotor speed, reaction time, and cognitive flexibility. This is reflected in longer on times (relative to off times) in both cases and controls, in both rounds.[23]

The common factors, linking achievement in Stroop on time and off time, are psychomotor speed and reaction time, and they have been shown to be compromised in patients undergoing endoscopy. Riphaus *et al.* demonstrated that sedation with midazolam and pethidine resulted in slowed reaction time and diminished psychomotor speed. They further showed that the midazolam and pethidine group had more lane deviations while driving, spent more time over the speed limit, and missed stoplights more often when compared to baseline and to propofol group. In contrast, psychomotor speed and driving skills returned to baseline 2 hours after endoscopy for subjects sedated with propofol.[20]

Our study showed that a majority of controls, if not all of them, and some cases, did better on the second round when compared to the first. This was thought to be due to familiarity with the test. Currently, there are no data standardizing the use of EncephalApp by testing subjects twice within a matter of an hour. Among cases, some of them did better on the second round in a few areas despite having undergone sedation for endoscopy. It is unclear if other studies, which also employed similar psychometric tests, took this factor into consideration when interpreting the results.

Patients who underwent procedures with sedation experienced slowed psychomotor speed, which is evident from slower off time and slower total time. However, cognitive flexibility appeared intact as there was no significant slowing of on time. Sedation did seem to impact reaction time and psychomotor speed, but cognitive flexibility returned to baseline.

A limitation of our study is that we were unable to show complete return of psychomotor speed and reaction time to baseline. Given the structure of current endoscopic practice, with patients being discharged home under the supervision of a family member, there was not enough time to delay the postprocedure app testing any more. It is possible that postprocedure testing at 1–2 hours after completion of procedure may confirm complete return of cognitive function to baseline. As noted above, patients who underwent endoscopy with Propofol had return of psychomotor speed and driving skills to baseline 2 hours after endoscopy.[20] If the post-testing was done 2 hours after endoscopy, our study would probably have shown complete or near-complete return of cognitive function to baseline. If established, this could reduce the need for patients to be escorted home.

CONCLUSION

Our study supports the return of cognitive flexibility to baseline within 30–45 min after propofol sedation for outpatient GI endoscopy despite delayed return of psychomotor speed and reaction time. This preliminary data suggests that patients could potentially drive or take public transportation without the need for an accompanying family member, if given enough time to recover after endoscopy, thus reducing the complexity of scheduling and cancellations for outpatient endoscopies. Additional studies are needed to determine the optimal timing of patient discharge so they can be allowed to leave without a companion.

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Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Cohen LB, Wecsler JS, Gaetano JN, Benson AA, Miller KM, Durkalski V, *et al.* Endoscopic sedation in the United States: Results from a nationwide survey. Am J Gastroenterol 2006;101:967-74.
2. Peery AF, Dellon ES, Lund J, Crockett SD, McGowan CE, Bulsiewicz WJ, *et al.* Burden of gastrointestinal disease in the United States: 2012 update. Gastroenterology 2012;143:1179-87.e1-3.
3. Faulx AL, Vela S, Das A, Cooper G, Sivak MV, Isenberg G, *et al.* The changing landscape of practice patterns regarding unsedated endoscopy and propofol use: A national Web survey. Gastrointest

Endosc 2005;62:9-15.
4. Zuccaro G Jr. Sedation and analgesia for GI endoscopy. Gastrointest Endosc 2006;63:95-6.
5. Practice guidelines for sedation and analgesia by non-anesthesiologists. Anesthesiology 2002;96:1004-17.
6. Rex DK. Review article: Moderate sedation for endoscopy: Sedation regimens for non-anaesthesiologists. Aliment Pharmacol Ther 2006;24:163-71.
7. Keeffe EB, O'Connor KW. 1989 A/S/G/E survey of endoscopic sedation and monitoring practices. Gastrointest Endosc 1990;36(3 Suppl):S13-8.
8. Ulmer BJ, Hansen JJ, Overley CA, Symms MR, Chadalawada V, Liangpunsakul S, *et al.* Propofol versus midazolam/fentanyl for outpatient colonoscopy: Administration by nurses supervised by endoscopists. Clin Gastroenterol Hepatol 2003;1:425-32.
9. Vargo JJ, Cohen LB, Rex DK, Kwo PY. Position statement: Nonanesthesiologist administration of propofol for GI endoscopy. Gastroenterology 2009;137:2161-7.
10. Wang D, Chen C, Chen J, Xu Y, Wang L, Zhu Z, *et al.* The use of propofol as a sedative agent in gastrointestinal endoscopy: A meta-analysis. PLoS One 2013;8:e53311.
11. Sethi S, Wadhwa V, Thaker A, Chuttani R, Pleskow DK, Barnett SR, *et al.* Propofol versus traditional sedative agents for advanced endoscopic procedures: A meta-analysis. Dig Endosc 2014;26:515-24.
12. Vargo JJ, Bramley T, Meyer K, Nightengale B. Practice efficiency and economics: The case for rapid recovery sedation agents for colonoscopy in a screening population. J Clin Gastroenterol 2007;41:591-8.
13. Fagà E, De Cento M, Giordanino C, Barletti C, Bruno M, Carucci P, *et al.* Safety of propofol in cirrhotic patients undergoing colonoscopy and endoscopic retrograde cholangiography: Results of a prospective controlled study. Eur J Gastroenterol Hepatol 2012;24:70-6.
14. Khamaysi I, William N, Olga A, Alex I, Vladimir M, Kamal D, *et al.* Sub-clinical hepatic encephalopathy in cirrhotic patients is not aggravated by sedation with propofol compared to midazolam: A randomized controlled study. J Hepatol 2011;54:72-7.
15. Riphaus A, Lechowicz I, Frenz MB, Wehrmann T. Propofol sedation for upper gastrointestinal endoscopy in patients with liver cirrhosis as an alternative to midazolam to avoid acute deterioration of minimal encephalopathy: A randomized, controlled study. Scand J Gastroenterol 2009;44:1244-51.
16. Disma N, Astuto M, Rizzo G, Rosano G, Naso P, Aprile G, *et al.* Propofol sedation with fentanyl or midazolam during oesophagogastroduodenoscopy in children. Eur J Anaesthesiol 2005;22:848-52.
17. Padmanabhan U, Leslie K, Eer AS, Maruff P, Silbert BS. Early cognitive impairment after sedation for colonoscopy: The effect of adding midazolam and/or fentanyl to propofol. Anesth Analg 2009;109:1448-55.
18. Wang D, Wang S, Chen J, Xu Y, Chen C, Long A, *et al.* Propofol combined with traditional sedative agents versus propofol- alone sedation for gastrointestinal endoscopy: A meta-analysis. Scand J Gastroenterol. 2013;48:101-10.
19. VanNatta ME, Rex DK. Propofol alone titrated to deep sedation versus propofol in combination with opioids and/or benzodiazepines and titrated to moderate sedation for colonoscopy. Am J Gastroenterol 2006;101:2209-17.
20. Riphaus A, Gstettenbauer T, Frenz MB, Wehrmann T. Quality of psychomotor recovery after propofol sedation for routine endoscopy: A randomized and controlled study. Endoscopy 2006;38:677-83.
21. Cohen LB, Hightower CD, Wood DA, Miller KM, Aisenberg J. Moderate level sedation during endoscopy: A prospective study using low-dose propofol, meperidine/fentanyl, and midazolam. Gastrointest Endosc 2004;59:795-803.
22. Allampati S, Duarte-Rojo A, Thacker LR, Patidar KR, White MB, Klair JS, *et al.* Diagnosis of minimal hepatic encephalopathy using stroop EncephalApp: A multicenter US-based, Norm-based study. Am J Gastroenterol 2016;111:78-86.
23. Bajaj JS, Thacker LR, Heuman DM, Fuchs M, Sterling RK, Sanyal AJ, *et al.* The Stroop smartphone application is a short and valid method to screen for minimal hepatic encephalopathy. Hepatology 2013;58:1122-32.
24. Reid MW, Cohen S, Wang H, Kaung A, Patel A, Tashjian V, *et al.* Preventing patient absenteeism: Validation of a predictive overbooking model. Am J Manag Care 2015;21:902-10.
25. Huang Y, Hanauer DA. Patient no-show predictive model development using multiple data sources for an effective overbooking approach. Appl Clin Inform 2014;5:836-60.