The primary purpose of this investigation was to evaluate postprocedure cognitive function associated with 3 distinct standard sedation regimens used for endoscopic procedures. A secondary aim was to identify complications requiring provider interventions. Subjects scheduled for colonoscopies were approached for enrollment the day of their procedure. A convenience sample of 96 subjects was randomly assigned. Cognitive function was recorded on the day of surgery using the Mini-Mental State Examination (MMSE) and 24 and 48 hours postoperatively using the Telephone Interview of Cognitive Status (TICS).

The propofol plus fentanyl group had a mean TICS score of 34.53 at 24 hours compared with 34.96 at 48 hours (P = .017). The midazolam plus fentanyl group had a mean TICS score of 34.76 at 24 hours compared with 36.26 at 48 hours (P = .004). The propofol-alone group had a mean TICS score of 35.98 at 24 hours compared with 35.98 at 48 hours (P = .924). The results of this investigation indicate that the sedation regimen of propofol alone has the least impact on postprocedure cognitive function. Additionally, the number of jaw lift interventions was significantly higher in both groups who received fentanyl.

Keywords: Colonoscopy, patient outcomes, physician outcomes, postoperative cognitive dysfunction, provider interventions.

C

onscious sedation is routinely performed in endoscopic procedures using various medication regimens. The ideal regimen of conscious sedation should provide adequate amnesia, analgesia, and tolerance for the patient throughout the procedure and should provide ease of instrumentation for the endoscopist. This ideal sedation regimen should also have a rapid onset and short duration of action, with minimal effects on postprocedure cognitive function. Many medication combinations can provide excellent sedation for a procedure; however, these combinations may alter postprocedure cognitive function, prolong recovery time, or require advanced training for the provider administering the sedation. Therefore, in conjunction with assessing postprocedure cognitive function, it is necessary to evaluate the depth of sedation and any hemodynamic or airway instability observed during medication administration. In addition, a measurement of satisfaction of both the provider and the patient to the medication regimen administered is also necessary.

There are many ways to define postoperative cognitive dysfunction (POCD). Newman et al\(^1\) described POCD as a significant change in cognition following a surgical procedure based on performance of specific neuropsychological tests, and which has been associated most often with cardiac surgery. Interestingly, the prevalence of POCD has primarily been studied in elderly patients undergoing cardiac surgery.\(^2\) For the purpose of this investigation, the definition of POCD described by Newman et al will be used as the operational definition of POCD.

Cohen et al\(^3\) evaluated cognitive dysfunction in patients presenting for endoscopic procedures in 2004. The purpose of their investigation was to systematically evaluate the depth of sedation obtained with a propofol protocol in patients undergoing endoscopy. The investigators concluded that a regimen of low-dose propofol plus midazolam plus an opioid would produce a moderate level of sedation consistent with the results seen with a standard-dose propofol regimen. These investigators also performed preprocedure and postprocedure neuropsychological testing using the Symbol Digit Test, the Stroop Color Word Test, and the Trail Making Tests. These neuropsychological tests revealed no significant difference in cognitive function.\(^3\)

Hennessy et al\(^4\) compared the postprocedure cognitive function associated with midazolam and diazepam in 30 patients undergoing esophagogastroduodenoscopy. This investigation, performed in 1990, revealed a sig-
nificant impairment of postprocedure recall of verbal, visual, and tactile stimuli with administration of either midazolam or diazepam. In addition, the midazolam group demonstrated significantly greater anterograde amnesia than in the diazepam group at equipotent doses. The investigators used these postprocedure cognitive assessments: Wechsler Memory Scale, Tactile Memory Test, Complex Figure Test, Oral Word Association Test, and Associative Learning Subtest. 4

Hennessy and associates used significantly greater amounts of midazolam and diazepam than did Cohen et al, who found no significant difference in cognitive function. This comparison suggests that the dose of a benzodiazepine may determine the extent of postprocedure cognitive dysfunction. However, it is not clear if the synergistic effects of other adjuncts, such as opioids and sedatives used during sedation, contribute to any postprocedure cognitive dysfunction.

For colonoscopy procedures it is important that the patient be lightly to moderately sedated, to facilitate patient cooperation and early identification of potential accidental bowel perforation. The American Society of Anesthesiologists (ASA) developed a scale to measure the depth of sedation for an operative procedure. The Depth of Sedation Scale consists of 3 levels: minimal, moderate, and deep. Deep anesthesia is not usually optimal for endoscopic sedation because it often requires a provider with specialized training to manage the patient’s hemodynamic status and to provide appropriate airway interventions. 5

Numerous medication regimens are currently used to perform endoscopic conscious sedation. Medications such as midazolam, diazepam, ketamine, fentanyl, meperidine, and propofol have all been used successfully, alone or in combination. This investigation used the 3 medication regimens most common to the facility where this investigation was performed. The 3 sedation regimens selected were as follows: (1) propofol alone, (2) propofol plus fentanyl, and (3) midazolam plus fentanyl.

A comprehensive literature review revealed research investigations that evaluated postprocedure cognitive function after conscious sedation for endoscopic procedures. Although POCD has been studied in other surgical populations, one possible explanation for the lack of literature regarding POCD studies after conscious sedation may be that investigators focused primarily on elderly patients and high-risk surgical procedures. Furthermore, depth of sedation provided by the sedation regimen, complications requiring provider interventions, and patient and physician satisfaction with the sedation regimen have not been extensively evaluated.

The primary purpose of this investigation was to detect whether there were differences in postprocedure cognitive function between the 3 selected sedation regimens. Secondary study objectives included comparing the depth of sedation obtained from the 3 regimens; evaluating provider interventions needed for the 3 sedation regimens; and evaluating the satisfaction of the sedation for both the patient and the physician performing the procedure.

Materials and Methods
On approval by the institutional review board at the National Naval Medical Center, Bethesda, Maryland, a prospective, randomized, single-blind investigation was conducted in the medical center’s gastroenterology clinic. A convenience sample of 96 adult male and female patients scheduled for colonoscopy was enrolled in this investigation.

A power analysis was conducted to assist in determining the sample size. The study used 3 ordinal groups for level of sedation (mild, moderate, and deep) and tested 3 groups for difference in proportion (propofol alone, propofol plus fentanyl, and fentanyl plus midazolam). The goal of this investigation was to test the research hypothesis that the proportion of cases falling into each sedation category (mild, moderate, and deep) is not identical for each treatment group (propofol alone, propofol plus fentanyl, and fentanyl plus midazolam). The criterion for significance (α) was set at .05 (2-tailed). An effect size of 0.373 was selected. This effect was selected as the smallest effect that would be important to detect, in the sense that any smaller effect would not be of clinical or substantive significance. It is also assumed that this effect size is reasonable, in that an effect of this magnitude could be anticipated in this field of research. The effect size hypothesized represents a good-faith estimate based on existing data, but given the exploratory nature of this study, it is possible that the true effect size may be larger or smaller than that hypothesized. Given the hypothesized effect size, a sample of 87 (29 per group) would provide a power level of 80.5% to yield a statistically significant result. Allowing for 10% attrition and/or missing data per group, the study authors attempted to enroll 32 subjects per group, for a total sample size of 96 subjects.

Inclusion criteria consisted of men and women scheduled for a colonoscopy who were ASA class 1 or 2. The minimum inclusion age was 18 years. Exclusion criteria included the following: patients unable to give informed consent; patients with hearing, visual, or communication impairments; patients with allergies to the medications used in the investigation; pregnant or breastfeeding women; and patients with a history of seizure disorders or sleep apnea.

Following informed consent, patients were randomly assigned to 1 of the 3 sedation regimen groups and asked to complete the demographic data collection sheet. All patients completed the Mini-Mental State Examination (MMSE) questionnaire for preassessment purposes in the preprocedure holding area. Intravenous access was obtained, and then the patient was taken to the procedure room. During the procedure, one investigator recorded the depth of anesthesia and provider interventions,
while another investigator administered the randomized sedation regimen. Since the 2 investigators would know the medication regimen used for each patient, the only investigator blinded to the medication regimen was the one who administered informed consent to the patient and who performed the cognitive test.

During the procedure, the investigators monitored provider interventions, including airway manipulations, maintenance of hemodynamics, treatment of oxygen desaturation, and the use of reversal agents for opioids and benzodiazepines. Airway manipulations included jaw lifts (placement of fingers behind the mandible to lift the jaw forward and relieve airway obstruction); realignment of the pharyngeal, oropharyngeal, and laryngeal axes (re-positioning the head to prevent airway obstruction and allow continued spontaneous ventilation of the patient); placement of an oropharyngeal airway to prevent the tongue from obstructing the airway; and advanced airway intervention requiring an intubation with an endotracheal tube or laryngeal mask airway. Both of the latter devices are used in general anesthetic techniques for provider-assisted ventilation. All required airway manipulations were counted and categorized.

The maintenance of hemodynamic stability was determined by the need to increase fluid administration or the administration of ephedrine or phenylephrine. The preceding interventions were conducted to ensure that the patient’s vital signs remained within 20% of their preprocedure or baseline measurement, to ensure stability of vital signs.

Treatment of oxygen desaturation included increasing the oxygen flow rate, changing the airway delivery device, or mask ventilation. The interventions were used to ensure an oxygen saturation of a minimum of 95% throughout the procedure.

After the patient was taken to the postanesthesia care unit, the endoscopist completed the Physician Outcomes Questionnaire to assess the level of provider satisfaction with the sedation regimen. Once patients met discharge criteria, they were instructed to complete the MMSE with the sedation regimen. Once patients met discharge criteria, they were instructed to complete the MMSE and the TICS are validated instruments that measure cognitive status. The MMSE contains 11 questions in 5 different areas of cognitive function: orientation; registration; attention and calculation; immediate and short-term recall; and language and praxis. The TICS contains 4 qualitative impairment ranges: unimpaired, ambiguous, mildly impaired, and moderately to severely impaired cognitive function. The highest score obtainable is 41. Cognitive impairment is determined by lower scores.

- **Intraprocedure data collection sheet.** The investigators developed an intraprocedure data collection sheet to document airway interventions, hemodynamic manipulations, treatment for oxygen desaturation, and use of a reversal agent for opioids or benzodiazepines.

- **American Society of Anesthesiologists Depth of Sedation Scale.** The Depth of Sedation Scale consists of 3 levels: minimal, moderate, and deep. A review of the literature found no data regarding the reliability and validity of the ASA Depth of Anesthesia Scale.

- **Iowa Satisfaction with Anesthesia Scale.** The ISAS was created to measure patient satisfaction during monitored anesthesia care. This 11-question instrument measures patient satisfaction using a Likert scale. Dexter et al measured the validity and internal consistency of the ISAS and found that the ISAS did have content validity and reliability.

- **Physician Outcomes Questionnaire.** Sipe et al developed the Physician Outcomes Questionnaire to evaluate the provider’s satisfaction with the sedation regimen administered for a colonoscopy. A review of the literature revealed no data regarding the reliability and validity of this questionnaire.

### Results

Ninety-six patients were enrolled in this investigation. Four patients were excluded from the final statistical analysis because they were unavailable for follow-up at the 24-hour or 48-hour reassessments. The 92 patients included met the 10% attrition rate for statistical analysis to ensure adequate power of the study.

Descriptive and inferential statistics were used to analyze demographic data. Mean continuous data were analyzed using 1-way analysis of variance (ANOVA). P values < .05 were considered significant. The demographic data are outlined in the Table. There was no significant difference in any demographic variables between the 3 sedation groups. Postprocedure cognitive function results from the MMSE and the TICS were analyzed using paired-samples tests.

No statistically significant differences were noted between the preassessment and discharge MMSE scores (Figure 1; \( P = .216 \) for propofol-alone group; \( P = .732 \) for propofol plus fentanyl group; \( P = .889 \) for fentanyl plus midazolam group).

A significant difference between the 24- and 48-hour...
TICS scores were noted in both the propofol plus fentanyl group and the fentanyl plus midazolam group. The propofol plus fentanyl group had a mean TICS score of 34.53 at 24 hours, and a mean score of 34.96 at the 48-hour assessment ($P = .017$). The fentanyl plus midazolam group had a mean TICS score of 34.76 at the 24-hour assessment, and a mean score of 36.26 at the 48-hour assessment ($P = .004$). The propofol-alone group had a mean TICS score of 35.09 at 24 hours, and a mean score of 35.98 at the 48-hour assessment ($P = .924$; Figure 2).

The amount of medication administered to each group was evaluated using ANOVA. There was a significant difference in the amount of fentanyl administered in the propofol-alone versus the propofol plus fentanyl group (70.6 μg vs 166.1 μg, respectively; $P < .001$). There was also a significant difference in the amount of propofol administered in the propofol-alone group, $P < .001$, and the propofol plus fentanyl group vs the propofol-alone group (249.1 mg vs 292.5 mg; $P < .00$).

Pearson $\chi^2$ tests were used to analyze provider interventions. A significant difference in the number of jaw lifts performed among the 3 sedation groups was noted. Jaw lifts occurred in the propofol plus fentanyl group 32.3% of the time and 25.8% of the time in the fentanyl plus midazolam group. Conversely, jaw lifts occurred in the propofol-alone group only 6.5% of the time. The difference was statistically significant for propofol alone compared with propofol plus fentanyl ($P < .01$) and also for propofol alone compared with fentanyl plus midazolam ($P < .038$; Figure 3).

Depth of sedation was measured with the ASA Depth of Sedation Scale. A significant difference was noted between the sedation groups at all measured time points (Figure 4).

The Kruskal-Wallis test was used to analyze patient satisfaction with the sedation regimen as measured by the ISAS. Responses to 2 statements at the 48-hour assessment were significantly different among groups. The statements were, “I threw up or felt like throwing up” and “I felt good.” Subjects in the fentanyl plus midazolam group reported feeling more nauseated ($P = .003$) and did not feel as “good” ($P = .001$) compared with the propofol-alone and propofol with fentanyl groups.

Provider satisfaction was measured with the Physician Outcomes Questionnaire. No significant difference was found among the 3 sedation regimens regarding this variable.

## Discussion

The present study compared 3 selected sedation regimens for endoscopic procedures—propofol alone, propofol plus fentanyl, and fentanyl plus midazolam—for their effect on postprocedure cognitive function. Additional comparisons included the depth of sedation, number of provider interventions, and patient and endoscopist satisfaction with sedation. Multiple investigations have evaluated the effectiveness for sedation of propofol and other adjuncts to include midazolam, meperidine, and fentanyl. However, few of these investigations have evaluated POCD following endoscopic procedures in the outpatient setting. This investigation demonstrated the administration of propofol alone had less effect on POCD at both 24 and 48 hours compared with the other 2 sedation regimens at similar depths of sedation.

In addition, fewer jaw lifts were required in the propofol-alone group compared with the 2 other sedation regimens that included fentanyl. Padmaabhan et al$^{11}$ compared early cognitive impairment after sedation for colonoscopy using the CogState brief computerized test battery and found that the addition of midazolam and/or fentanyl to propofol sedation did not result in more cognitive impairment compared with propofol alone. Furthermore, the use of adjuncts improved the ease of colonoscopy without increasing the rate of complications or prolonging early recovery times.$^{11}$ The present investigation found a significant difference in POCD in the 24-hour TICS assessment compared with the 48-hour TICS assessment in both the propofol plus fentanyl group and the fentanyl plus midazolam group, but not in the propofol-alone group. However, the baseline MMSE and the discharge MMSE scores demonstrated no significant difference for any of the 3 groups. This finding suggests that when fentanyl is added to the sedation regimen, cognitive function may be minimally impaired for at least the first 24 hours after the procedure. Of note, no significant differences were found with the discharge MMSE scores. A possible explanation for this finding is that the MMSE is less sensitive compared with TICS for evaluating cognitive function in patients who have received sedation.

In this investigation, larger doses of propofol were administered when propofol was used alone without adjuncts. The addition of fentanyl to propofol significantly reduced the total amount of propofol used compared

<table>
<thead>
<tr>
<th>Propofol alone</th>
<th>Propofol plus fentanyl</th>
<th>Fentanyl plus midazolam</th>
</tr>
</thead>
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<tr>
<td>Age, y (mean)</td>
<td>54.5</td>
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</tr>
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<td>Weight, kg (mean)</td>
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<tr>
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<tr>
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<td>17/13</td>
</tr>
<tr>
<td>No. of subjects</td>
<td>31</td>
<td>30</td>
</tr>
</tbody>
</table>

Table. Demographic Characteristics
with the propofol-alone group. VanNatta and Rex found similar results when they compared the use of propofol alone to propofol plus opioids and/or benzodiazepines. However, the study by VanNatta and Rex did not separate the propofol plus opioid group from the propofol plus benzodiazepine group. Therefore, that study did not determine whether fentanyl is more synergistic than midazolam, thus requiring less propofol to be administered.

In this investigation the propofol-alone group required significantly fewer provider interventions than the propofol plus fentanyl group and the fentanyl plus midazolam group. In a similar study by Paspatis et al, synergistic effects with midazolam and propofol vs midazolam and meperidine revealed that of 3 patients needing provider interventions, 2 of the patients were in the midazolam and meperidine group and only 1 was in the propofol and midazolam group. The investigation demonstrated less cognitive impairment in the propofol and midazolam group.

The ISAS analysis indicated that more patients in the fentanyl plus midazolam group rated nausea higher and feeling good lower than did the other 2 groups with propofol. This is similar to the results that the Paspatis team obtained. However, Padmanabhan et al found that nausea in 20% of the propofol-alone group was rated as “fair” compared with only 10% of the patients in the groups receiving propofol plus adjuncts.

In addition to measuring patient satisfaction, our investigation also measured the satisfaction of the endosco-

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**Figure 1. MMSE Results**

Abbreviation: MMSE, Mini-Mental State Examination.

*No statistically significant differences were seen between baseline and after discharge.*

**Figure 2. TICS Results**

Abbreviation: TICS, Telephone Interview for Cognitive Status.

*Propofol-alone: P = .924; propofol plus fentanyl: P = .017; fentanyl plus midazolam: P = .004.*

**Figure 3. Number of Patients Requiring Jaw Lifts**

*Propofol-alone vs propofol + fentanyl: P < .01; propofol-alone vs fentanyl + midazolam: P < .038.*

**Figure 4. Depth of Sedation Level**

Abbreviation: Scope, endoscope.
pist performing the procedure. We found no significant difference in endoscopists’ satisfaction among the 3 sedation regimens.

In this study, the depth of anesthesia was recorded using the ASA Depth of Anesthesia Scale. The participants were categorized as mildly, moderately, or deeply sedated. At several predetermined time intervals throughout the procedure, depth of anesthesia was measured and recorded. At every time interval with the exception of the start of the case, the fentanyl plus propofol group measured at the deeply sedated level, whereas the propofol-alone and fentanyl plus midazolam groups measured at the moderately sedated level. Conversely, Padmanabhan et al,11 using the observer’s assessment of alertness/sedation score and bispectral index score, determined that all 3 of their groups were similarly sedated. Similarly, Paspatis et al13 also determined that there was no significant difference in sedation between their 2 groups of participants using a sedation score ranging from 5 (not arousable) to 1 (fully awake).

This study had several limitations. First, the patients recruited were classified as having ASA 1 and ASA 2 status. Most community hospitals may perform colonoscopies on patients with more comorbidities that could require additional provider interventions and therefore increase the incidence of POCD. Second, the use of the MMSE and TICS for POCD assessment could have had an impact on the results because the patients developed a learning effect by being exposed to the same questions numerous times. Therefore, subsequent investigations might need to reassess the use of the MMSE and TICS for POCD assessment or use another instrument that measures cognitive function. Third, the need to contact the participants at 24- and 48-hour intervals and for them to have a responsible person with them to assist with the questionnaire became problematic and time-consuming. Although the patients were contacted on the first and second postprocedure days, the time was not always at the 24- and 48-hour interval because of patient unavailability.

Conclusion
This investigation found that the administration of propofol alone resulted in the least impact on POCD at both 24- and 48-hour assessments compared with the propofol plus fentanyl and the midazolam plus fentanyl groups. The propofol-alone group required significantly fewer jaw lifts from the provider than did the propofol plus fentanyl and fentanyl plus midazolam groups. The depth of sedation was significantly different for all groups at all measured times. Patients in the propofol plus fentanyl group and the midazolam plus fentanyl group were more deeply sedated. Finally, no significant differences in patient or physician satisfaction among the sedation groups were revealed.

Overall, the results of this investigation suggest that the sedation regimen of propofol alone, compared with the other regimens studied, provides adequate sedation with minimal effects on POCD and limits the number of provider interventions. Based on the findings of this investigation, propofol alone may be the optimal anesthetic regimen for colonoscopy procedures.

REFERENCES

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DISCLAIMER

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