Effective Dosage of Midazolam to Erase the Memory of Vascular Pain During Propofol Administration

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Intravenous sedation with propofol is often administered to anxious patients in dental practice. Pain on injection of propofol is a common adverse effect. This study aimed to determine the age-adjusted doses of midazolam required to erase memory of vascular pain of propofol administration and assess whether the Ramsay Sedation Scale (RSS) after the pretreatment of midazolam was useful to predict amnesia of the vascular pain of propofol administration. A total of 246 patients with dental phobia requiring dental treatment under intravenous sedation were included. Patients were classified according to their age: 30s, 40s, 50s, and 60s. Three minutes after administration of a predetermined dose of midazolam, propofol was infused continuously. After completion of the dental procedure, patients were interviewed about the memory of any pain or discomfort in the injection site or forearm. The dosage of midazolam was determined using the Dixon up-down method. The first patient was administered 0.03 mg/kg, and if memory of vascular pain remained, the dosage was increased by 0.01 mg/kg for the next patient, and then if the memory was erased, the dosage was decreased by 0.01 mg/kg. The effective dosage of midazolam in 95% of each age group for erasing the memory of propofol vascular pain (ED_{95}) was determined using logistic analysis. The accuracy of RSS to predict the amnesia of injection pain was assessed by receiver operating characteristic (ROC) analysis. The ED_{95} of midazolam to erase the memory of propofol vascular pain was 0.061 mg/kg in patients in their 30s, 0.049 mg/kg in patients in their 40s, 0.033 mg/kg in patients in their 50s, and 0.033 mg/kg in patients in their 60s. The area under the ROC curve was 0.31. The ED_{95} of midazolam required to erase the memory of propofol vascular pain demonstrated a downward trend with age. On the other hand, it was impossible to predict the amnesia of propofol vascular pain using the RSS.

Key Words: Midazolam; Propofol; ED_{95} ; Vascular pain.

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Propofol is one of the most commonly used sedative agents for intravenous sedation during dental procedures. By continuous infusion, propofol provides the ability to titrate to a desired level of sedation and

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provides a rapid recovery because of the short context-sensitive half-time and the short effect-site equilibration time.¹ However, propofol causes a high incidence of pain on injection, approximately 60% according to a recent review, with some patients recalling the induction of anesthesia as the most painful part of the perioperative period.² Various methods of reducing vascular pain caused by propofol have long been the subject of investigation. Some reports have stated that a mixed injection with lidocaine is effective.^{3,4} Although intravenous lidocaine (0.5 mg/kg) with a rubber tourniquet on the forearm 30–120 seconds before the injection of propofol has been considered the most effective technique, the efficacy rate is only approximately 60%;⁴ therefore, it has not become standard practice. Furthermore, propofol is prepared in a micellar state, and the micellar diameter reportedly increases with time following mixing with lidocaine solution.⁵ Because a pulmonary embolism can be caused when the micellar diameter exceeds 4–5 μm , mixing propofol with lidocaine solution is not a clinically useful method unless the combination is used soon after mixing.⁶

Jalota et al² recommended the routine use of small doses of opioid before induction of anesthesia despite lesser efficacy than the lidocaine-tourniquet technique. However, opioids should be administered carefully because of potential ventilation concerns for dental outpatients when intravenous conscious sedation is the intended level of sedation.

Intravenous sedation is often administered to anxious patients in dental practice. For these patients, fear and anxiety about pain on injection of sedation medication may have a great impact on such patients. We believe that erasing the negative memory of the painful injection of propofol is therefore important. Ideally, sedation providers would like to either predict the susceptibility to propofol injection pain or prevent it completely.

Midazolam has a great advantage in eliminating unpleasant perioperative memories because of its strong anterograde amnesic properties. Furthermore, in addition to its anxiolytic effect, intravenous preadministration of midazolam has been reported to reduce postoperative nausea and vomiting and increase patient satisfaction.⁷ Thus, these secondary effects can also be advantageous in improving the patient's perioperative experience. Pretreatment with midazolam may also be useful to erase the memory of propofol injection pain. Earlier studies demonstrated that intravenous midazolam 2 mg prior to a propofol infusion decreased recollection of uncomfortable intraoperative events, including pain on propofol injection.⁸ On the other hand, because it is well known that elderly patients are more sensitive to the sedative action of midazolam compared with younger patients,^{9,10} determining the age-adjusted dose of mid-

Table 1. Ramsay Sedation Scale

1. Patient is anxious and agitated or restless, or both
2. Patient is cooperative, oriented, and tranquil
3. Patient responds to commands only
4. Patient exhibits brisk response to light glabellar tap or loud auditory stimulus
5. Patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus
6. Patient exhibits no response

azolam for amnesia for propofol injection pain would be beneficial. The purpose of this study was to determine the effective dosage of midazolam in 95% of an age-adjusted population for erasing the memory of propofol injection pain. We also assessed whether the Ramsay Sedation Scale (RSS; see Table 1) after the pretreatment of midazolam was useful to predict amnesia of the pain of injection of propofol.

METHODS

Study Design

After approval from the Institutional Review Board and Ethical Committee of Osaka University Dental Hospital (H24-E12), this study was registered with the UMIN Clinical Trials Registry (UMIN000009894). Written informed consent was obtained from 246 patients, aged 30–69 years, with ASA physical status 1 or 2, undergoing dental procedures of less than 60 minutes under intravenous sedation from February 2013 to March 2014. Exclusion criteria were the following: allergy to propofol, soybean or egg; significant obesity (body mass index of 30 or higher); and use of sedative drugs.

Study Protocol

Patients were classified into 4 groups according to age: patients in their 30s, 40s, 50s, and 60s. As is customary in our institution, patients were nothing per os (NPO) for 4 hours for conscious sedation. On patients' arrival at the treatment room without preanesthetic medication, a 22-gauge cannula was inserted into the largest and straightest antecubital vein available and a predetermined dose of midazolam was administered. Three minutes later, the level of sedation was assessed using the RSS (Table 1). We chose 3 minutes, as in a previous pilot study we found that some patients were too sedated for effective verbal communication if we waited longer than 4 minutes after administration of midazolam. Then, we informed the patient about the start of propofol

The Flow Diagram of this study

Figure 1. The flow diagram of this study.

administration and propofol (Maruishi Pharmaceutical) was injected continuously at a rate of 3 mg/kg/h (50 mcg/kg/min). Patients were then tapped on their shoulder gently and asked if they felt vascular pain during the propofol injection. At this point, patients were sedated essentially by midazolam only; the sedation level at that time was RSS 2 or 3, so verbal communication was possible. Patients were kept sedated until completion of surgery with a continuous infusion of propofol at 2–4 mg/kg/h. The intended sedation level with this continuous infusion of propofol was considered moderate as described by the American Society of Anesthesiologists.¹¹ Patients were then kept at an adequate sedation level (RSS 3 or 4) during the dental procedure by adjustment of the infusion rate of propofol. After completion of surgery, patients who complained of vascular pain were interviewed by a research team

member who was blinded to dose of midazolam. Patients were asked about the memory of pain or discomfort at the injection site or forearm. In the present study, patients who received propofol and complained of vascular pain were assessed of their memory and patients who did not complain of vascular pain were excluded from data analysis.

The dosage of midazolam was determined using the modified Dixon up-down method.¹² A dose of 0.03 mg/kg of midazolam was administered to the first patient in each age group and if memories of injection pain remained, the dosage was increased by 0.01 mg/kg for the second patient, and then if memories were erased, the dosage was decreased by 0.01 mg/kg. The maximum dose of midazolam was set at 0.08 mg/kg, as in Japan, the maximum dose of midazolam as a single bolus administration is 5 mg. In each age group, this

Table 2. Patient Demographics*

	30s	40s	50s	60s	<i>P</i> Value
Sex, male/female	10/18	9/19	8/12	9/17	NS
Height, cm	162.5 ± 8.5	162.2 ± 7.3	163.7 ± 8.2	160.2 ± 8.3	NS
Weight, kg	57.9 ± 10.6	59.8 ± 10.2	59.8 ± 10.2	56.5 ± 12.6	NS

* Data are expressed as mean ± SD. NS indicates not significant.

process was repeated until 15th crossover points,¹³ where all independent pairs of patients manifested a crossover from residual memories to memory loss or the reverse, were obtained. In addition, we assessed cutoff values for RSS to erase memory of injection pain using a receiver operating characteristic (ROC) curve.

Throughout the sedation, heart rate, oxygen saturation, and arterial blood pressure were monitored and supplemental oxygen (3 L/min via a nasal cannula) was administered.

Statistical Analysis

In a pilot study, approximately 40% of patients complained of propofol vascular pain on injection in each age group (each group $n = 10$). Estimated sample size was calculated based on the results of this pilot study. It was determined that we needed approximately 60 patients in order to get the 15th crossover points from the 40% of patients who complained of propofol vascular pain in each age group.

Logistic regression analysis was used for statistical processing to compare each age group and calculations of effective dosage of midazolam in 95% of each group (ED_{95}). A P value of $<.05$ was considered to indicate statistical significance. We also conducted an assessment using an ROC curve to investigate cutoff values for the level of sedation required to erase memories of propofol vascular pain on injection.

RESULTS

A flow diagram of the conduct of the study is shown in Figure 1. Of the 261 patients who were initially assessed, 246 patients were allocated to 4 groups according to their age, and 102 patients successfully completed the study without any complication.

Table 2 shows demographic characteristics of the patients who were analyzed. There were no significant differences in sex, height, or weight among the 4 groups.

Table 3 shows the presence or absence of pain at the time of propofol injection. The numbers of patients who complained of pain were 28 (for patients in their 30s),

28 (for patients in their 40s), 20 (for patients in their 50s), and 26 (for patients in their 60s).

Figures 2 through 5 show the consecutive dose of midazolam required to erase the memory of injection pain for each age group according to the up-down method.

The predictive ED_{95} of midazolam (dose mg/kg [95% CI]) required to erase the memory of injection pain calculated by the logistic regression analysis was 0.061 (0.047–0.304) mg/kg for patients in their 30s, 0.049 (0.038–0.163) mg/kg for patients in their 40s, 0.033 (0.028–0.067) mg/kg for patients in their 50s, and 0.033 (0.027–0.085) mg/kg for patients in their 60s (Figure 6). The amount of midazolam required to erase the memory of propofol injection pain demonstrated a downward trend with age, although there were no significant differences among the 4 groups (Table 4). Figure 7 shows the ROC curve produced by RSS at the time of propofol injection as independent variable and the presence or absence of memory of injection pain as the outcome based on data from all patients. The area under the curve (AUC) was 0.31, which shows that RSS was not a reliable predictor of amnesia.

After the administration of midazolam, oxygen saturation transiently dropped below 95% in 1 patient in the 40s, 1 patient in the 50s, and 3 patients in the 60s; however, this reduction was immediately improved in all patients by asking them to take a deep breath. All patients responded appropriately. There were no serious complications during the sedation.

DISCUSSION

Vascular pain at the time of propofol injection is a side effect associated with anesthesia that should be avoided.¹⁴ An explanation of vascular pain that occurs at the

Table 3. Number of Patients Who Complained of Presence or Absence of Pain at the Time of Propofol Injection

	Presence of Pain, No. (%)	Absence of Pain, No. (%)	Total
30s	28 (42)	38 (58)	66
40s	28 (44)	35 (56)	63
50s	20 (38)	32 (62)	52
60s	26 (40)	39 (60)	65

Figure 2. The consecutive dose of midazolam according to the up-down method for patients in their 30s. The number of patients required to get the 15th crossover point (•→○ or ○→•) was 28. If memories of injection pain remained (•), the dosage was increased by 0.01 mg/kg for the next patient, and then if memories were erased (○), the dosage was decreased by 0.01 mg/kg.

time of propofol injection should be given during the preanesthetic evaluation to minimize patient anxiety. Because erasing the memory of pain at the time of injection may prevent interference with the next anesthetic encounter for the patient in question or prevent communication of this adverse event with other patients, it is considered highly significant.

Memories typically consist of the acquisition, retention, and reproduction of information and are classified into short-term memories,¹⁵ where information is retained for less than 1 hour, and long-term memories, where information is retained for longer than 1 hour. Short-term memory is thought to be necessary in the acquisition of long-term memories.¹⁶

A previous study performed using intravenously administered midazolam (0.01, 0.02, 0.04, and 0.08 mg/kg) in order to erase the memory of lumbar puncture pain reported that short-term memories could be suppressed in a dose-dependent manner up to 20 minutes after administration of midazolam.¹⁷ This suggested that if we would like to prohibit the acquisition of an unpleasant memory, the unpleasant action should take place within 20 minutes of the administration of midazolam. In our study, we started administering propofol 3 minutes after administering midazolam. Therefore, our method had a reasonable likelihood of prohibiting the acquisition of the unpleasant memory of propofol vascular pain on injection.

Figure 3. The consecutive dose of midazolam according to the up-down method for patients in their 40s. The number of patients that was required to get the 15th crossover point (•→○ or ○→•) was 28. If memories of injection pain remained (•), the dosage was increased by 0.01 mg/kg for the next patient, and then if memories were erased (○), the dosage was decreased by 0.01 mg/kg.

Figure 4. The consecutive dose of midazolam according to the up-down method for patients in their 50s. The number of patients that was required to get the 15th crossover point (•→○ or ○→•) was 20. If memories of injection pain remained (•), the dosage was increased by 0.01 mg/kg for the next patient, and then if memories were erased (○), the dosage was decreased by 0.01 mg/kg.

In the present study, the incidence of pain of propofol injection was lower than has been previously reported. The incidence of pain on propofol injection is estimated to be around 70% in the setting of general anesthesia.⁴ On the other hand, Kwon et al¹⁸ reported that the intensity of injection pain appeared to be relatively mild during intravenous sedation for upper gastrointestinal endoscopy. We also had the same impression as Kwon et al¹⁸ during intravenous sedation for dental procedures. Although the reason for this difference is not yet understood, the rate and dose of propofol administration may be a determining factor. Picard and Tramèr⁴ determined from 56 randomized controlled trials during general anesthesia that the rate of propofol administra-

tion (mean rate 6 mg/s; range, 0.125–20 mg/s) had no impact on the incidence of pain. However, because the induction of general anesthesia requires a deeper level of sedation than that of intravenous sedation, a larger dose of propofol must be injected rapidly. In the present study, propofol was injected at a rate of approximately 0.05 mg/s and the initial propofol dose was so small that the incidence and intensity of injection pain would be expected to be lower and milder.

Midazolam has a strong anterograde amnesic effect as well as a hypnotic effect. In the present study, age-adjusted doses of midazolam (ED₉₅) required to erase the memory of injection pain were determined by logistic regression analysis and declined with increasing patient

Figure 5. The consecutive dose of midazolam according to the up-down method for patients in their 60s. The number of patients that was required to get the 15th crossover point (•→○ or ○→•) was 26. If memories of injection pain remained (•), the dosage was increased by 0.01 mg/kg for the next patient, and then if memories were erased (○), the dosage was decreased by 0.01 mg/kg.

Figure 6. Effective dosage of midazolam in 95% of each age group (ED₉₅) required to erase the memory of injection pain calculated by logistic regression analysis. ED₉₅ was 0.061 (95% CI, 0.047–0.304) mg/kg in patients in their 30s, 0.049 (95% CI, 0.038–0.163) mg/kg in patients in their 40s, 0.033 (95% CI, 0.028–0.067) mg/kg in patients in their 50s, and 0.033 (95% CI, 0.027–0.085) mg/kg in patients in their 60s. The left end of the graph indicates the lower end of 95% CI and the right end indicates the upper end of 95% CI. The amount of midazolam required to erase the memory of injection pain demonstrated a downward trend with age, although there were no significant differences among the 4 groups.

age. Bell et al¹⁹ also found a relatively linear decrease in midazolam required for sedation for upper gastrointestinal endoscopy with age. Jacobs et al¹⁰ reported that the steady-state plasma midazolam concentration at which 50% of patients would be expected not to respond to verbal command decreased with age because of increased pharmacodynamics sensitivity. Our results also reflect the effects of age on the amnestic effect of midazolam.

Although Nagahama et al^{17,20} have reported that a small bolus administration of midazolam (0.03 or 0.06 mg/kg) provided enough amnesia and sedation without any adverse effects for spinal anesthesia, no regard was given to the effects of aging on midazolam dose. Boku et al¹³ measured doses of midazolam required for loss of memory during lumbar spinal puncture in 50% of patients (0.043 mg/kg for patients in their 50s, 0.035 mg/kg for patients in their 60s, and 0.026 mg/kg for patients in their 70s) and concluded that aging increased sensitivity to the amnestic effects of midazolam. This report supports our result that the ED₉₅ of midazolam decreases with age.

In the present study, we evaluated RSS for determining amnesia for propofol injection pain by calculating the AUC in ROC analysis in distinguishing between presence and absence of vascular pain. The calculated AUC was only 0.31 and the optimal cutoff value was not obtained. The calculated AUC of 0.31 means low correlation accuracy. Therefore, it is unpredictable to use RSS as an indicator of amnesia of propofol vascular

pain. According to the study by Matsuki et al,²¹ a large distribution of bispectral index (BIS) value was seen within each sedation level on the RSS, with BIS values overlapping each other. There was such a wide range in sedation level in each RSS that we could not get an accurate cutoff value of RSS. On the other hand, there are some reports of a good relationship between amnesia and BIS value. Glass et al²² reported that 50% of healthy volunteers demonstrated a complete lack of recall at BIS values ranging from 84 to 86. Nakasuji et al²³ recommended a BIS value below 90 to get amnesia of pain during lumbar epidural puncture with midazolam. The BIS value may be superior to the RSS for evaluating level of sedation and may enable anesthesiologists to predict amnesia during propofol injection.

Side effects associated with administration of midazolam include respiratory depression and oversedation. Although 4 patients experienced a transient decrease in

Table 4. The Results of Logistic Analysis*

Parameter	Estimate	SE	Chi-Square	P value
30s vs 40s	−0.43	0.33	1.66	.1977 NS
30s vs 50s	−0.81	0.43	3.59	.058 NS
30s vs 60s	−0.96	0.45	4.63	.0315 NS
40s vs 50s	−0.27	0.36	0.55	.4596 NS
40s vs 60s	−0.46	0.36	1.66	.1981 NS
50s vs 60s	−0.39	0.42	0.86	.3533 NS

* An accurate *P* value using Bonferroni analysis is .0083. There were no differences among the groups. NS indicates not significant.

Figure 7. The receiver operating characteristic (ROC) curve produced by RSS. The area under the curve (AUC) was 0.31. It is indicated by the gray zone, which shows that RSS was not a reliable predictor of amnesia.

oxygen saturation following administration of midazolam, it was improved quickly by arousal of the patient. No patients in any of the age groups experienced oversedation as a result of midazolam administration. The combination technique of midazolam and propofol has some advantages. Midazolam is reported to exert a synergistic effect when coadministered with propofol,²⁴ which is associated with a high degree of patient comfort and rapid recovery time.⁸ A combined sedation regimen may be superior to sedation with propofol alone in terms of recovery, side effects, and costs because of a possibly lower total amount of propofol needed. However, Fanti et al²⁵ reported that premedication with a low dose of midazolam does not reduce the total amount of propofol administered.²⁵ However, Seifert et al²⁶ reported that sedation with propofol and midazolam required a lower total dose of propofol, but otherwise has no superior sedation efficacy and is associated with a slower postprocedure recovery than sedation with propofol alone.

Future studies should evaluate the presence or absence of memory of propofol vascular pain on injection using BIS values instead of RSS for conscious sedation.

CONCLUSIONS

Although there were no significant differences in the ED₉₅ of midazolam required to erase the memory of propofol vascular pain on injection, we demonstrated a downward trend in dosage with age (0.061 mg/kg in patients in their 30s, 0.049 mg/kg in patients in their 40s, 0.033 mg/kg in patients in their 50s, and 0.033 mg/kg in patients in their 60s). It was not possible to predict the amnesia of injection pain from the sedation level assessed by RSS.

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REFERENCES

1. Bryson HM, Fulton BR, Faulds D. Propofol. An update of its use in anaesthesia and conscious sedation. *Drugs*. 1995; 50:513–559.
2. Jalota L, Kalira V, George E, et al. Perioperative clinical research core. Prevention of pain on injection of propofol: systematic review and meta-analysis. *BMJ*. 2011;342:d1110.
3. Ishiyama S, Yamamoto H, Yamakage M, Namiki A. Propofol in an emulsion of long- and medium-chain triglycerides reduces the incidence and intensity of pain on injection in adults. *J Clin Anesth (Jpn)*. 2003;27:1725–1730.
4. Picard P, Tramèr MR. Prevention of pain on injection with propofol: a quantitative systematic review. *Anesth Analg*. 2000;90:963–969.
5. Lillet EM, Isert PR, Carasso ML, Kennedy RA. The effect of the addition of lidocaine on propofol emulsion stability. *Anesthesia*. 1996;51:815–818.
6. Masaki Y, Tanaka M, Nishikawa T. Physicochemical compatibility of propofol-lidocaine mixture. *Anesth Analg*. 2003;97:1646–1651.
7. Bauer KP, Dom PM, Ramirez AM, O'Flaherty JE. Preoperative intravenous midazolam: benefits beyond anxiolysis. *J Clin Anesth*. 2004;16:177–183.
8. Taylor E, Ghouri AF, White PF. Midazolam in combination with propofol for sedation during local anesthesia. *J Clin Anesth*. 1992;4:213–216.
9. Platten HP, Schweizer E, Dilger K, Mikus G, Klotz U. Pharmacokinetics and the pharmacodynamic action of midazolam in young and elderly patients undergoing tooth extraction. *Clin Pharmacol Ther*. 1998;63:552–560.
10. Jacobs JR, Reves JG, Marty J, White WD, Bai SA, Smith LR. Aging increases pharmacodynamic sensitivity to the

hypnotic effects of midazolam. *Anesth Analg*. 1995;80:143–148.

11. American Society of Anesthesiologists. Continuum of depth of sedation: definition of general anesthesia and levels of sedation/analgesia. Approved by ASA House of Delegates on October 13, 1999, and last amended on October 15, 2014. Schaumburg, Ill.: American Society of Anesthesiologists; 2014.

12. Dixon WJ. Staircase bioassay: the up-and-down method. *Neurosci Biobehav Rev*. 1991;15:47–50.

13. Boku A, Koyama S, Kishimoto N, et al. Examination of the optimal midazolam dose required for loss of puncture memory at the time of spinal anesthesia. *Masui*. 2011;8:913–919.

14. Koitabashi T, Innami Y, Ouchi T, Uemura N. Age difference as related to the incidence and severity of propofol injection pain. *J Clin Anesth (Jpn)*. 2004;10:1657–1661.

15. McGaugh JL. Memory—a century of consolidation. *Science*. 2000;287:248–251.

16. Hazama H, Kawahara T. Obstacle of short-term memory by record benzodiazepine medicine manufacturing (triazolam). *Seishin Igaku*. 1981;23:361–365.

17. Nagahama H, Kikuchi S, Shimazaki K, Tateda T, Aoki T, Takahashi K. The use of low dose midazolam for the management of spinal anesthesia. *Masui*. 1996;45:593–598.

18. Kwon JS, Kim ES, Cho KB, et al. Incidence of propofol injection pain and effect of lidocaine pretreatment during upper gastrointestinal endoscopy. *Dig Dis Sci*. 2012;57:1291–1297.

19. Bell GD, Reeve PA, Moshiri M, et al. Intravenous midazolam: a study of the degree of oxygen desaturation occurring during upper gastrointestinal endoscopy. *Clin Pharmacol*. 1987;23:703–708.

20. Nagahama H, Okada Y, Kinouchi H, Tateda T, Aoki T, Morokawa Y. The use of low dose midazolam for the management of spinal anesthesia. *Masui*. 1997;46:803–808.

21. Matsuki Y, Ichinohe T, Kaneko Y. Amnesia for electric dental pulp stimulation and picture recall test under different levels of propofol or midazolam sedation [published online ahead of print November 21, 2006]. *Acta Anaesthesiol Scand*. 2007;51:16–21.

22. Glass PS, Bloom M, Kears L, Rosow C, Sebel P, Manberg P. Bispectral analysis measures sedation and memory effects of propofol, midazolam, isoflurane, and alfentanil in healthy volunteers. *Anesthesiology*. 1997;86:836–847.

23. Nakasuji M, Nakamura T, Imanaoka N, et al. Bispectral index during epidural puncture predicts anterograde amnesia in patients given midazolam premedication. *J Anesth*. 2009;23:329–333.

24. Reimann FM, Samson U, Derad I, Fuchs M, Schiefer B, Stange EF. Synergistic sedation with low-dose midazolam and propofol for colonoscopies. *Endoscopy*. 2000;32:239–244.

25. Fanti L, Agostoni M, Arcidiacono PG, et al. Target-controlled infusion during monitored anesthesia care in patients undergoing EUS: propofol alone versus midazolam plus propofol. A prospective double-blind randomized controlled trial [published online ahead of print October 16, 2006]. *Dig Liver Dis*. 2007;39:81–86.

26. Seifert H, Schmitt TH, Gültekin T, Caspary WF, Wehrmann T. Sedation with propofol plus midazolam versus propofol alone for interventional endoscopic procedures: a prospective, randomized study. *Aliment Pharmacol Ther*. 2000;14:1207–1214.