Mild Sedation Exacerbates or Unmasks Focal Neurologic Dysfunction in Neurosurgical Patients with Supratentorial Brain Mass Lesions in a Drug-specific Manner

Nan Lin, M.D., Ruquan Han, M.D., Ph.D., Jianxin Zhou, M.D., Adrian W. Gelb, M.B.Ch.B.

ABSTRACT

Background: Sedation is commonly used in neurosurgical patients but has been reported to produce transient focal neurologic dysfunction. The authors hypothesized that in patients with frontal–parietal–temporal brain tumors, focal neurologic deficits are unmasked or exacerbated by nonspecific sedation independent of the drug used.

Methods: This was a prospective, randomized, single-blind, self-controlled design with parallel arms. With institutional approval, patients were randomly assigned to one of the four groups: "propofol," "midazolam," "fentanyl," and "dexmedetomidine." The sedatives were titrated by ladder administration to mild sedation but fully cooperative, equivalent to Observer's Assessment of Alertness and Sedation score = 4. National Institutes of Health Stroke Scale (NIHSS) was used to evaluate the neurologic function before and after sedation. The study's primary outcome was the proportion of NIHSS-positive change in patients after sedation to Observer's Assessment of Alertness and Sedation = 4.

Results: One hundred twenty-four patients were included. Ninety had no neurologic deficits at baseline. The proportion of NIHSS-positive change was midazolam 72%, propofol 52%, fentanyl 27%, and dexmedetomidine 23% (P less than 0.001 among groups). No statistical difference existed between propofol and midazolam groups (P = 0.108) or between fentanyl and dexmedetomidine groups (P = 0.542). Midazolam and propofol produced more sedative-induced focal neurologic deficits compared with fentanyl and dexmedetomidine. The neurologic function deficits were mainly limb motor weakness and ataxia. Patients with high-grade gliomas were more susceptible to the induced neurologic dysfunction regardless of the sedative.

Conclusions: Midazolam and propofol augmented or revealed neurologic dysfunction more frequently than fentanyl and dexmedetomidine at equivalent sedation levels. Patients with high-grade gliomas were more susceptible than those with low-grade gliomas. **(Anesthesiology 2016; 124:598-607)**

REPEATED neurologic evaluation is a necessity for hospitalized patients with central nervous system disorders to identify global and/or focal changes requiring treatment. Neurosurgical patients undergo routine neurologic examinations preoperatively in the ward, sometimes in the operating room, and then in the postanesthesia care unit and intensive care unit.[1,2] Sedation is commonly used in these locations. In clinical practice, sedatives with different mechanisms of action are widely used to produce the desired sedation.[3] However, in clinical trials of such drugs, patients with neurologic disorders are specifically excluded.

Twenty-five years ago, Cucchiara[4] observed a phenomenon that some neurosurgical patients awakening from anesthesia presented focal neurologic deficits but recovered to normal over a relatively short time, referring to it as "differential awakening." There have been subsequent case reports and small studies suggesting effects of anesthetics, sedatives, and analgesics resulting in transient neurologic dysfunction in patients with vulnerable central nerve systems.[5–11] These have included patients with stroke or transient ischemia attack, spondylosis, and brain tumors including awake craniotomy. Such unanticipated effects may leave caregivers bewildered by unexplained (postoperative) neurologic deficits and

What We Already Know about This Topic

- In neurosurgical patients, administration of sedative agents can unmask latent neurologic deficits or can exacerbate pre-existing deficits
- Whether exacerbation of deficits is due to nonspecific sedation or due to a drug-specific effect is not clear
- The authors compared the effect of sedation with propofol, midazolam, fentanyl, and dexmedetomidine on clinical neurologic deficits in patients with brain mass lesions

What This Article Tells Us That Is New

- Mild sedation with propofol and midazolam exacerbated neurologic deficits to a greater extent than fentanyl or dexmedetomidine; the latter had the least effect on neurologic function
- The change in neurologic function in patients with pre-existing brain lesions is a drug-specific effect and is not due to nonspecific sedation

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Submitted for publication May 11, 2015. Accepted for publication November 20, 2015. From the Department of Anesthesiology (N.L., R.H.) and Department of Critical Care Medicine (J.Z.), Beijing Tiantan Hospital, Capital Medical University, Beijing, China; Department of Anesthesia and Perioperative Care, University of California San Francisco, San Francisco, California (A.W.G.).

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result in excessive clinical and neuroimaging examinations and may be of great concern to patient and family. Conversely, some experienced neurosurgeons assume that unexpected neurologic changes,[4] especially in the immediate perioperative period, are an effect of the anesthetic drugs and choose to wait and see what happens.

However, those case reports and small studies offer no insight into frequency, predisposing factors, or drug dose specificity. Therefore, it is important to determine these differences in patients with brain mass lesions because it may influence drug choice and also the interpretation of the clinical findings. Currently, the main four agents used perioperatively in neurosurgical patients include the benzodiazepine midazolam, the anesthetic hypnotic propofol, the narcotic fentanyl, and the α2-agonist dexmedetomidine.[12,13] In this study, we used these drugs that act at different receptors or subunits but that were titrated to the same sedation level in patients with supratentorial, intracranial mass lesions to determine whether they have comparable effects on neurologic signs as assessed by National Institutes of Health Stroke Scale (NIHSS). We hypothesized that in patients with frontal–parietal–temporal brain mass lesions, focal neurologic deficits are unmasked or exacerbated by nonspecific sedation, that is, sedation produced by any mechanism.

Materials and Methods

This prospective, single-center, randomized, single-blind (patient-blind) parallel arm study was carried out in the neurosurgical operation room in Beijing Tiantan Hospital, Capital Medical University, Beijing, China. The study protocol and the consent form were approved by the Institutional Review Board of Beijing Tiantan Hospital, Capital Medical University (approval number kylw-2010-017-02). The study was registered and approved by the Chinese Clinical Trial Registry (Chinese Clinical Trial Registry, ChiCTR-TRC-13003774, PI: Nan Lin, Date of Registration: November 11, 2013, http://www.chictr.org.cn/showproj.aspx?proj=5786).

Elective neurosurgery patients at a very busy neurosurgical hospital with supratentorial mass lesions (frontal–parietal–temporal regions) diagnosed by magnetic resonance imaging (MRI) were eligible for this study. Patients were included if they were between 18 and 65 yr old and with American Society of Anesthesiology (ASA) status I–II. Institutional approval and informed consent were required for all the patients. The exclusion criteria were as follows: pregnant and/or lactating women, recurrent brain tumor, unable to comprehend and cooperate with the neurologic examination, impaired mental status, taking sedative drugs orally or intravenously in the past 24 h, taking any analgesics orally or intravenously in the past 24 h, and drug and/or alcohol abuse. The latter were all based on the hospital record documentation.

Patients who met the protocol criteria were randomly assigned to one of the four intervention study groups, labeled "propofol group," "fentanyl group," "midazolam group," or "dexmedetomidine group." Randomization was based on a computer-generated random digits table. Permuted block randomization was used with a block size of 4 and an allocation ratio of 1:1:1:1. Because all four sedatives have very different times to peak effect varying from 2 to 10 min (*e.g.*, there is only 1 to 2 min time delay with propofol but 7 to 10 min time delay with dexmedetomidine) and, manifestations after the administration are also different, the evaluating person could not be blinded. Investigators were blinded to the MRI report till the evaluation finished. Crossover was not allowed in this study and is reported as a protocol violation.

Neurologic Evaluation

NIHSS was used to evaluate the neurologic function. It scores consciousness, visual function, facial and motor function, ataxia, sensory and language function, and attention. The total score ranges from 0, no deficit, to a maximum of 42. A detailed explanation and score sheet can be found online.[14] First (baseline), NIHSS evaluation was evaluated before any medication, then all the patients were randomized and sedation was titrated with one of the four sedatives: propofol, midazolam, fentanyl, or dexmedetomidine. The patients' sedation level was evaluated by Observer's Assessment of Alertness/Sedation (OAA/S) scale that was developed to measure the level of alertness in subjects who are sedated.[15] The OAA/S is scored from 1 to 5, indicating deep sleep to fully alert (5 = alert, 4 = lethargic, 3 = aroused by voice, 2 = aroused by shaking, 1 = deep sleep). The titrated sedative doses were guided by OAA/S, targeting a score of 4. Once achieved, the second and if necessary the third NIHSS evaluation were done. Sedation level was also monitored by bispectral index (BIS). The whole study was completed before anesthesia induction. All neurologic assessments were performed by the same individual (N.L.) who had completed the NIHSS training. The study design is shown in figure 1.

Drug Administration Strategy

The initial bolus dose for propofol was 0.5 mg/kg, midazolam 0.03 mg/kg, fentanyl 2 μg/kg, and dexmedetomidine 0.3 μg/kg (infusion over 7 to 10 min). If OAA/S did not reach 4, one or two additional doses were given to try and achieve OAA/S = 4. There is a range of sedative doses that will achieve a sedation level of OAA/S = 4. Because we started with very small doses, it was possible that OAA/S = 4 was achieved but did not result in an NIHSS change (except NIHSS item 1, level of consciousness). Therefore, half of the initial dose was given so as to maintain OAA/S = 4 while increasing central nervous system drug concentration to see whether this induced an NIHSS change (except item 1). We tested the feasibility of this protocol in a pilot study. Those patients were not included in the final study. The details of the trial design are shown in figure 1.

The intervention was stopped if any of the following occurred: systolic blood pressure less than 90 mmHg or more

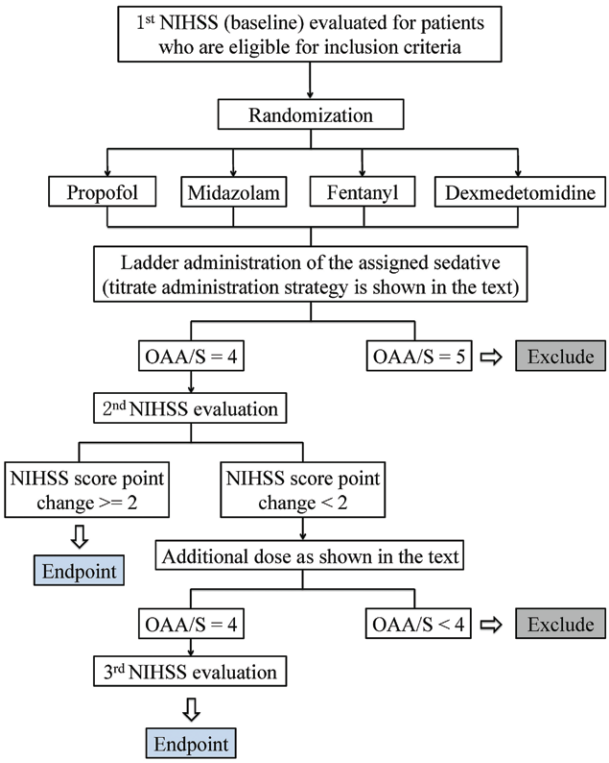

Fig. 1. Trial design for neurologic function evaluation after sedation. The sedative administration strategy is shown. The target sedation level was Observer's Assessment of Alertness/Sedation (OAA/S) = 4. All the patients who were less sedated (OAA/S = 5) or oversedated (OAA/S < 4) after the drug administration were excluded. The third National Institutes of Health Stroke Scale (NIHSS) was the last evaluation, no matter whether the score changed or not.

than 180 mmHg after the sedatives; heart rate less than 50 beats per minute (bpm) after 0.5 mg atropine; oxygen saturation less than 90%; over sedated as indicated by OAA/S equal or less than 3; inadequate sedation (OAA/S = 5) after maximum doses of sedatives; and any other sedative-related side effect such as respiratory depression, unstable hemodynamics, or agitation.

Study Endpoints

Primary Endpoints. The study's primary endpoints were the NIHSS score changes after the sedation to OAA/S = 4. The NIHSS level of consciousness item indicates an altered level of consciousness, which overlaps the OAA/S score. Therefore, a change in any other item indicated a focal neurologic function change (including visual, facial palsy, motor function, sensory function, limb ataxia, and language function). When analyzing NIHSS score change, we divided patients into "NIHSS-positive" and "NIHSS-negative" groups. NIHSS positive was defined as a score change greater than or equal to 2 after sedative administration, whereas NIHSS negative was defined as a score change less than 2 after sedative administration. A score of 2 therefore indicates 1 point for change in the level of consciousness (sedation) and 1 point for an additional deficit.

Secondary Endpoints. Blood pressure, heart rate, oxygen saturation, and BIS[16] were recorded, as well as the sedation level before and after sedative titration. The total dose of each sedative was noted. Other drugs used during the sedatives administration (name and dose) and any side effect were recorded and described. The percentage of cases with sedation-related NIHSS score change in each group was calculated. The clinical presentation regarding the neurologic diseases was obtained from the medical record and summarized. Preoperative brain MRI details were recorded, including the description of lesion location, size, midline shift, intracranial ventricular expansion or compression, peritumor edema, and hemorrhage. For patients with seizures, the details of the anticonvulsant drug use were recorded. Pathologic diagnosis 2 weeks after operations was also recorded.

Sample Size Justification

On the basis of a previous small neurological function evaluation study in which overall 30% of patients had exacerbation or unmasking of focal neurologic deficits after the sedatives,[6] the proportion of NIHSS-positive change in one group was assumed to be 30% under the null hypothesis and 75% under the alternative hypothesis. The significant level of the test was targeted at 0.05, and the statistical power was 90%. The test statistic used was the two-sided Z test with pooled variance. Sample size was calculated by PASS11.0.2 (Copyright ©1983–2011, NCSS Statistical Software, USA).

The minimum number of cases was 24 in one group that achieved 92% power to detect a possible statistical proportion difference between any of the two groups. Considering the possibility of early termination during the study and allowing 20% for a dropout rate, we raised this number to 34 subjects for each group. As four different sedatives were to be studied, we aimed to enroll at least 136 subjects.

Statistical Analysis

Kolmogorov–Smirnov test was used for evaluating whether the continuous variables were normally distributed or not. The normally distributed data were described as mean and SD with paired Student's t test to compare the parameters before and after medication. The nonnormally distributed data are presented as median and interquartile range and Kruskal–Wallis test was used for the data analysis. For categorical variables, numbers and percentage were described; χ^2 or Fisher's Exact Test was used to analyze differences among groups according to the group size. To analyze the NIHSS score before and after sedation, Wilcoxon signed-rank test was used. The nature of the testing was two-tailed. The significance level was adjusted to 0.008 applying the Bonferroni correction to adjust for the six comparisons of the primary outcome among the four groups. Analyses were conducted using Statistical Package for the Social Sciences (SPSS) version 17.0 (USA).

Results

One hundred forty-three patients were evaluated for eligibility between April and August 2013. Eight patients were excluded

after the initial assessment (fig. 2). One hundred thirty-five consented patients were randomized into propofol, midazolam, fentanyl, or dexmedetomidine groups according to a computer-generated randomization sequence. Eleven patients were excluded during the allocation and follow-up (fig. 2). In the dexmedetomidine group, one patient was excluded as the tumor was found to be in the insular at surgery, which was not consistent with the MRI diagnosis. There were 31 patients in the propofol group, 32 in the midazolam group, 30 in the fentanyl group, and 31 in the dexmedetomidine group who completed the study and were included for the analysis (fig. 2).

Physiological Parameter Changes

The total titrated dose of sedatives for mild sedation in both NIHSS-positive and -negative change groups was comparable (table 1). Mean arterial pressure was reduced from 100 (12) mmHg to 90 (11) mmHg after propofol administration (95% CI, −15.0 to −6.9 mmHg; *P* less than 0.001); for patients who received midazolam, blood pressure dropped from 102 (13) mmHg to 94 (10) mmHg (95% CI, −10.4 to −3.4 mmHg; *P* less than 0.001); fentanyl (*P* = 0.592) and dexmedetomidine (*P* = 0.185) changed blood pressure less than 3% of baseline. Heart rate was slightly decreased in the propofol group from 78 (16) bpm to 74 (13) bpm (95% CI, −7.0 to −0.6 bpm; *P* = 0.02) and significantly decreased in dexmedetomidine group from 77 (14) bpm to 61 (11) bpm (95% CI, −19.0 to −12.4 bpm; *P* less than 0.001). Fentanyl (*P* = 0.055) and midazolam (*P* = 0.897) changed heart rate less than 4% of baseline. Pulse oxygen saturation remained above 96% in all patients. BIS decreased by 20 (8) in propofol, 21 (7) in midazolam, 18 (6) in fentanyl, and 24 (10) in dexmedetomidine groups from baseline but increased back to the baseline as soon as patients were spoken to.

Sedative-induced NIHSS Score Change

Sedative-induced NIHSS Score Change and Proportion. All the sedatives generated NIHSS changes after the administration as shown in table 2. The majority of patients (90 of 124) had NIHSS baseline of 0, that is, no deficits, some had 1 point, only a few had more than 2 points, but the median score increased after sedation in each group. Wilcoxon signed-rank test showed a statistical difference between before and after sedatives; however, only if NIHSS change was equal or more than 2 points (including 1 point change in the level of consciousness), which was defined as positive change. All the sedatives generated NIHSS changes after the administration, the proportions of NIHSS-positive change in each sedative group are shown in figure 3, and there was a statistical difference among the groups (Pearson $\chi^2_{df=3} = 20.286$; *P* less than 0.001). However, no statistical difference existed between propofol and midazolam groups ($\chi^2_{df=1} = 2.741$; $P = 0.098$) or between fentanyl and dexmedetomidine groups ($\chi^2_{df=1} = 0.137$; $P = 0.711$). Between propofol and fentanyl, the odds ratio (OR) was 2.9 (95% CI, 1.0 to 8.6), propofol–dexmedetomidine OR was 3.6 (95% CI, 1.2 to 11.0), midazolam–fentanyl OR was 7.0 (95% CI, 2.3 to 21.5), and the OR between midazolam and dexmedetomidine was 8.8 (95% CI, 2.8 to 27.4).

Items Score Changes in NIHSS after Mild Sedation. Score changes in the 11-item NIHSS were evaluated. The majority of score changes were in limb motor function, where the point score ranges from 0 to 4 indicating "normal" to "no movement," respectively, in each limb for each patient and ataxia

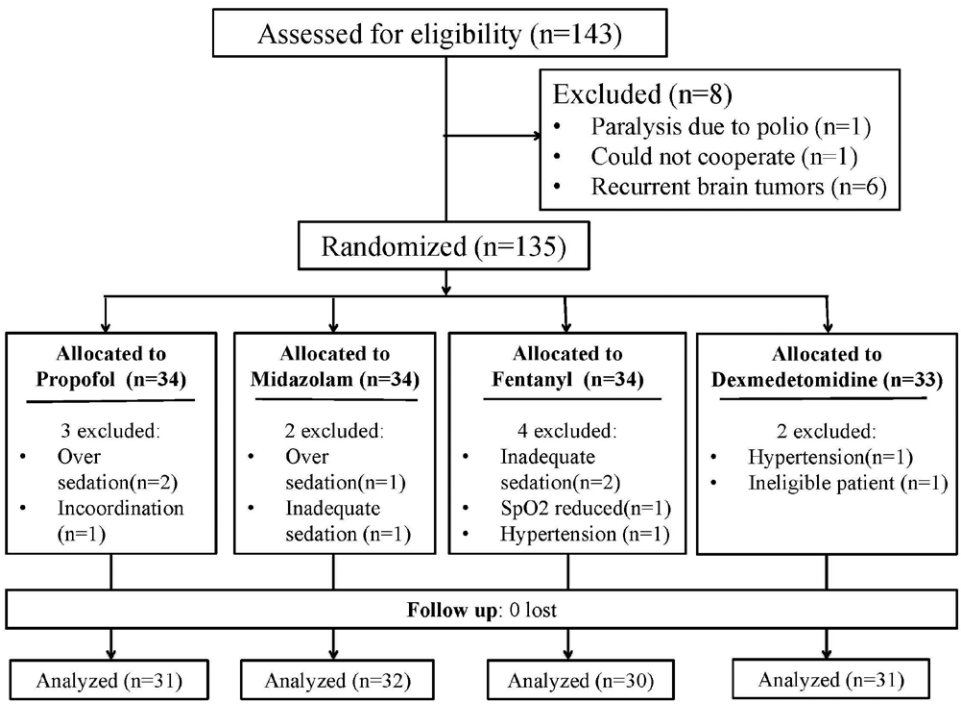

Fig. 2. The flow diagram of the study.

Table 1. Total Dose of Sedative (Mean (SD)) in NIHSS-positive and -negative Groups (OAA/S = 4)

	NIHSS Positive*	NIHSS Negative†	t Value	*P* Value
Propofol (mg)	60 (24.4)	68 (24.4)	−0.92	0.365
Midazolam (mg)	3 (1.2)	4 (0.9)	−1.351	0.187
Fentanyl (μg)	247 (60.0)	259 (84.0)	−0.374	0.711
Dexmedetomidine (μg)	44 (9.8)	44 (14.4)	−0.039	0.969

t Test did not show any statistical dose difference between the groups.
*NIHSS positive is defined as the score change ≥2 after sedative administration.†NIHSS negative is defined as the score change <2 after sedative administration.
NIHSS = National Institutes of Health Stroke Scale; OAA/S = Observer's Assessment of Alertness and Sedation score.

Table 2. NIHSS before and after Sedatives Titrated to Observer's Assessment of Alertness/Sedation (OAA/S) = 4

	NIHSS Score			Wilcoxon Signed-rank Test	
	Before Sedation	After Sedation	Score Change	Z Value	*P* Value
Propofol	0 [0–1]	2 [1–4]	2 [1–3]	−4.945	<0.001*
Midazolam	0 [0–0.75]	3 [1–5]	3 [1–4.75]	−4.97	<0.001*
Fentanyl	0 [0–1]	1 [1–2]	1 [1–2]	−5.025	<0.001*
Dexmedetomidine	0 [0–1]	1 [1–2]	1 [1–1]	−5.155	<0.001*

The score is shown as median [interquartile range].
*Wilcoxon signed-rank test showed statistical difference before and after sedation.
NIHSS = National Institutes of Health Stroke Scale.

(0 to 2 score point indicating "ataxia absent" and "ataxia" in two limbs). All the sedatives induced statistically significant limb motor score changes—midazolam group (from baseline score median [interquartile range] of 0 [0, 0] to 2 [1, 2]; Wilcoxon rank analysis; $P = 0.001$), propofol group (from 0 [0 to 0] to 2 [1 to 2]; $P = 0.002$), fentanyl group (from 0 [0 to 0.75] to 1.5 [1 to 3.5]; $P = 0.023$), and dexmedetomidine group (0 [0 to 0] to 1 [1 to 2]; $P = 0.024$). In addition, there were limb motor score change differences among the four sedatives (Kruskal–Wallis test, $\chi^2_{df=3} = 20.736$; P less than 0.001). For limb ataxia, propofol (from baseline score of 0 [0 to 0] to 1 [0 to 2]; Wilcoxon rank; $P = 0.006$) and midazolam (0 [0 to 0] to 1 [0 to 1.5]; Wilcoxon rank; $P = 0.001$) sedation induced significant score changes but with no statistical difference between those groups (Mann–Whitney U; $P = 0.420$). Fentanyl (from baseline score of 0 [0 to 0.25] to 0 [0 to 2]; Wilcoxon rank; $P = 0.180$) and dexmedetomidine (0 [0 to 0.5] to 0 [0 to 1]; Wilcoxon rank; $P = 0.317$) did not affect limb ataxia. The number of patients with induced changes for each item in the NIHSS is shown in figure 4. Midazolam induced the highest number of item changes, and dexmedetomidine induced the least number of item changes.

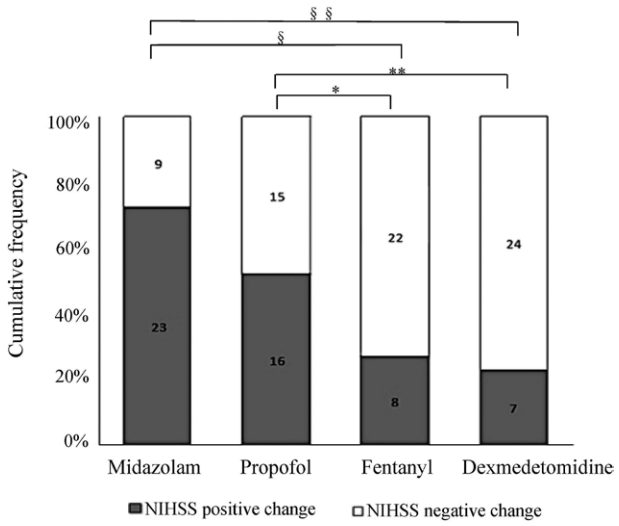

Fig. 3. The cumulative frequency and the number of cases with National Institutes of Health Stroke Scale (NIHSS) changes after midazolam, propofol, fentanyl, and dexmedetomidine titrated to Observer's Assessment of Alertness/Sedation = 4. NIHSS-positive change is defined as a score change ≥2 after sedative administration; NIHSS-negative change is defined as a score change <2 after sedative administration. $*\chi^2_{df=1} = 4.444$, $P = 0.035$; $**\chi^2_{df=1} = 7.177$, $P = 0.007$; $§\chi^2_{df=1} = 13.067$, $P < 0.001$; $§§\chi^2_{df=1} = 17.143$, $P < 0.001$.

Twelve patients had induced language comprehension changes or dysarthria, of which five were with midazolam, one with propofol, four with fentanyl, and two with dexmedetomidine. In the two patients with prior language comprehension deficits, one was worsened by fentanyl and another's comprehension function was not changed but dysarthria was induced by propofol. Other patients who showed sedation-related language deficits were function intact before being given any sedatives. The tumor size in patients whose language function was affected was 57.3 ± 12.7 mm, whereas the tumor size in patients without language deficits was 50.5 ± 17.8 mm (one-way ANOVA; $P = 0.201$).

Sedative-induced Focal Neurologic Changes and Patients' Characteristics

Sedative-induced NIHSS Score Change and Neurologic Deficits History. The presenting neurologic symptoms of the patients are shown in table 3. Patients with preoperative

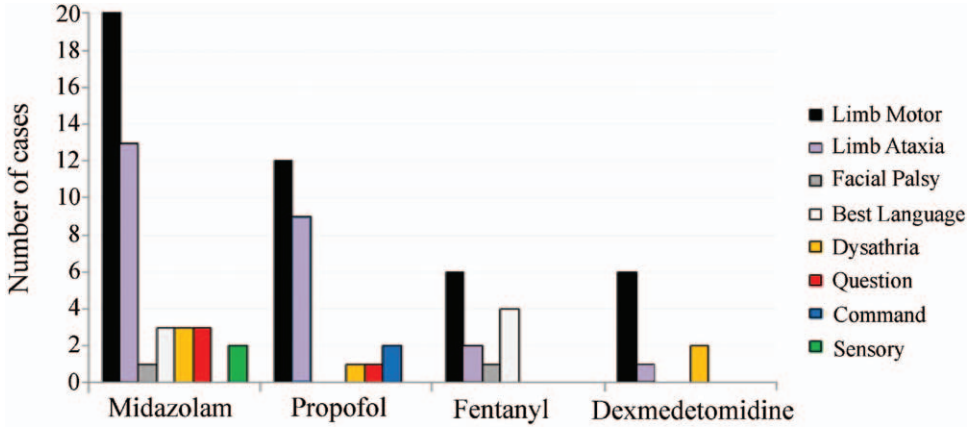

Fig. 4. The number of patients with changes for each item in the National Institutes of Health Stroke Scale induced by sedatives. All the patients experienced a level of consciousness item score change of 1.

motor deficits had more sedative-induced NIHSS-positive changes than those without, but only fentanyl and dexmedetomidine groups were statistically significant (fig. 5). For patients with no history of motor deficits, 18 of 27 subjects in midazolam and 14 of 28 subjects in propofol groups had sedation-related NIHSS-positive changes, and the proportions in fentanyl (4 of 25) and dexmedetomidine (3 of 25) groups were very much smaller (fig. 5). Thus, the effects of midazolam (Fisher exact test; $P = 0.288$) and propofol ($P = 1.000$) are not statistically influenced by the presence of motor deficits, whereas fentanyl ($P = 0.011$) and dexmedetomidine ($P = 0.014$) primarily affect patients with motor deficits. The NIHSS-negative change group had more seizure patients compared with the positive change group. Other neurologic symptoms did not affect the NIHSS-positive change incidence (table 3).

Sedative-induced NIHSS Score Change and Pathology. Seventy-seven patients had gliomas, 37 meningiomas, and 7 with other types of brain tumors, 1 metastatic tumor and 2 brain hematomas. All four sedative groups contained both gliomas (22 midazolam, 18 propofol, 18 fentanyl, and 19 dexmedetomidine) and meningiomas (9 midazolam, 11 propofol, 9 fentanyl, and 8 dexmedetomidine). There was no difference in sedative-induced NIHSS-positive changes between gliomas and meningiomas ($\chi^2_{df=1} = 0.203$; $P = 0.652$).

Further analysis showed that for patients who had a high-grade glioma (N = 20), all the sedatives could induce an NIHSS-positive change and there was no statistical difference among drugs (χ^2 test: $\chi^2_{df=3} = 5.145$; $P = 0.161$). Conversely, when sedated by dexmedetomidine, none of the 12 patients with low-grade gliomas had NIHSS changes (fig. 6).

Sedative-induced NIHSS Score Change and MRI Manifestation. The MRI was lost for one of the midazolam group. There was no relation between tumor size and neurologic change in any group. Brain mass lesions always involved frontal–parietal–temporal lobes but in some cases also involved other cerebral locations in addition. The relation between tumor location and neurologic change were as follows (number of positive change cases *versus* negative change): primary motor area (18 *vs.* 2), sensory area (10 *vs.* 4), language area (6 *vs.* 8), premotor area (4 *vs.* 8), insular lobe (4 *vs.* 6), corpus callosum (6 *vs.* 5), cingulate gyrus (1 *vs.* 1), basal ganglion (1 *vs.* 2), and internal capsule (4 *vs.* 0). The Fisher exact analysis showed that fentanyl-induced NIHSS-positive change occurred more frequently in eloquent area-affected patients ($P = 0.003$). If sedated by dexmedetomidine, NIHSS-positive change was significantly more frequent in patients with midline shift ($P = 0.028$).

Discussion

The main findings of this prospective randomized study of four commonly used sedatives were that mild sedation by midazolam and propofol are more likely to cause sedative-induced focal neurologic deficits compared with fentanyl and dexmedetomidine in patients with supratentorial mass lesion. Thus, our hypothesis of a nonspecific sedative effect was not upheld. The unmasked or exacerbated neurologic function deficits were mainly limb motor dysfunction and ataxia. Furthermore, our study showed that patients with high-grade gliomas were more susceptible to sedation-induced neurologic dysfunction regardless of the sedative, whereas dexmedetomidine did not affect function if the glioma was low grade. MRI results did not predict the changes in neurologic function in our study.

The NIHSS was developed for and is extensively used in stroke trials.[17] It has been found to be reliable for non-neurologists to use, in multiple languages, in the context of clinical trials.[18] The Chinese Putonghua version of NIHSS has been validated.[19] NIHSS can be rapidly learned through an online training program (Available at: https://secure.trainingcampus.net/uas/modules/trees/windex.aspx?rx=nihss-english.trainingcampus.net). In essence, the scale is a detailed, systematic neurologic examination and therefore can also be used in other patient populations where a reproducible neurologic examination is needed,[20] such as our study. The OAA/S was described for and has been

Table 3. Neurologic History

Symptoms	Frequency N (%)	NIHSS-positive Change, N	NIHSS-negative Change, N	χ^2 Value	*P* Value
Normal physical examination	13 (10.4)	6	7	0.04	0.841
Headache and dizziness	55 (44.0)	26	29	0.558	0.455
Seizure	49 (39.2)	16	33	3.912	0.048*
Sensory deficits	12 (9.6)	5	7	0.019	0.89
Motor deficits	19 (15.2)	15	4	11.437	0.001*
Visual deficits	6 (4.8)	4	2	1.43	0.401
Facial palsy	5 (4.0)	4	1	2.816	0.166
Language deficits	3 (2.4)	1	2	0.13	1
Memory decline	5 (4.0)	2	3	0.027	1

Patients may have single or combined neurologic symptoms. Patients who had routine examination had no neurologic symptoms.
*The Chi-square test and Fisher exact test showed statistical significance.
NIHSS = National Institutes of Health Stroke Scale.

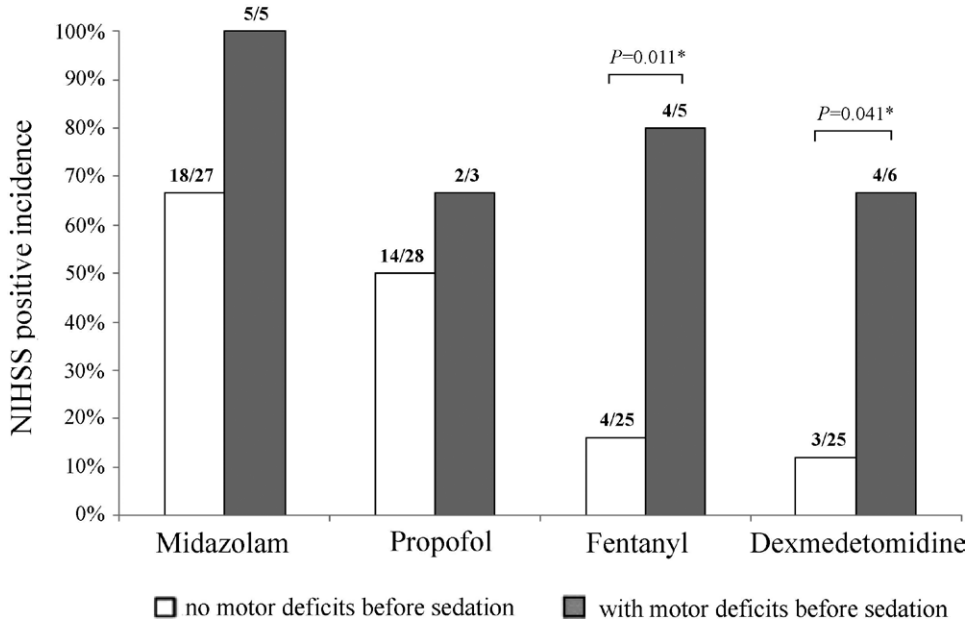

Fig. 5. The percentage of patients with National Institutes of Health Stroke Scale (NIHSS) change ≥2 after sedation titrated to Observer's Assessment of Alertness/Sedation = 4 in patients with or without motor function deficits before sedation. The denominator above each bar are the total number of cases in that bar, and the numerator is the number of cases with NIHSS-positive changes. *The statistical significance.

extensively used for assessing drug-induced sedation,[15] making it an appropriate scale for our study. In our study, there was always an NIHSS score change of 1 because the level of consciousness changed in all the patients who achieved OAA/S 4. We therefore only regarded an NIHSS score change of 2 or more as indicative of focal neurologic function change.

The hypothesis of this study was that the emergence or worsening of neurologic features would reflect a nonspecific sedative effect. For this to be true, at comparable levels of sedation, there should be similar changes in neurologic function independent of drug. This was not the case. For example, there was three times the number of midazolam patients with a score change compared with fentanyl and four times as many as dexmedetomidine. This indicates that there is drug specificity in the extent to which neurologic function is altered. Our study did not specifically investigate the mechanisms for the changes in neurologic function, so we can only speculate. It is clear that sedation alone is not the mechanism, given our findings of differences among the agents at the same level of sedation. Brain reorganization as a consequence of the tumor may alter regional blood flow and metabolism, and these could in some way account for the differences, perhaps by increasing drug delivery, slowing washout, or increasing metabolic suppression.[21] However, more likely explanations are a change in the synaptic and intracortical connectivity and receptor density or functionality as a result of the remodeling.[22] Additional support for the potential interaction with remodeling comes from the

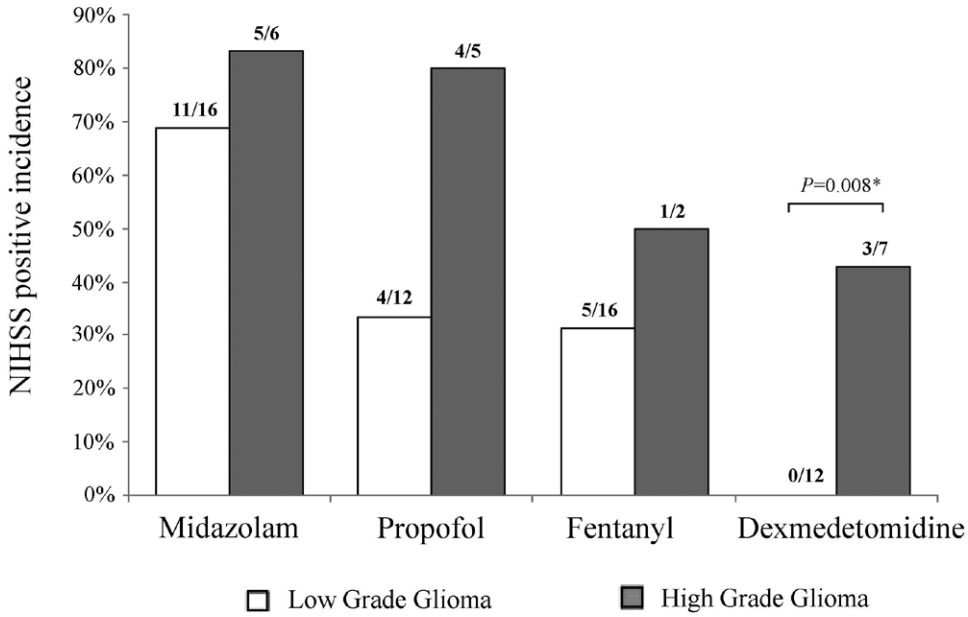

Fig. 6. The National Institutes of Health Stroke Scale (NIHSS)-positive incidence in patients with low or high-grade glioma after sedation by different sedatives. *Statistical significance by the Fisher exact testing.

fact that many patients did not have focal neurologic dysfunction, despite the lesion being near eloquent areas but had induced deficits after sedative exposure. The brain had presumably compensated for the tumor growth, but this compensation was then "suppressed" by the drugs.[23,24] Further complicating mechanistic speculation is the fact that drugs may have direct effects on a receptor population, for example, γ-aminobutyric acid-A receptors of various subtypes (propofol and midazolam) and also secondary effects. For example, fentanyl alters acetylcholine and dopamine release, which are two important neurotransmitters associated with brain reorganization and postinjury plasticity.[25–33] Similarly, propofol, through GABAergic mechanisms, alters dopamine and serotonergic activity.[34,35] Dexmedetomidine produced the least effects of the four sedatives and did not change focal function at all in patients with low-grade gliomas. This could be because of its highly selective effects subcortically in the locus coeruleus to achieve sedation. Specifically designed studies will be needed to clearly elucidate mechanism.

For all four sedatives, patients with high-grade gliomas were more likely than those with low-grade gliomas to have drug-induced deficits. Thus, drug effects were not an independent factor as tumor grade also defined the sensitivity to drugs. This possibly reflects the greater tissue destruction with a more malignant lesion and that the slower growing low-grade lesion allows better functional compensation but may also be related to the dynamics of tumor growth and tumor location,[36–38] the specific hemisphere,[21] and whether associated with interhemispheric connections.[23,24,39,40]

Our findings may also be particularly relevant for "awake" craniotomy surgery where patients are usually sedated or anesthetized before the awake testing period. A prospective clinical trial found that cognitive and motor performance was influenced by intraoperative sedation or total intravenous anesthesia).[41] Despite the study being predominantly performed in non-neurosurgical patients, their results support our findings. For patients with brain tumors, especially in close proximity to eloquent brain areas, cortical function may be worsened by (residual) sedation, particularly if midazolam or propofol are used. If our results apply intraoperatively, then dexmedetomidine with an opioid may be a preferred choice in terms of interference with neurologic function.

Limitations

There are a number of limitations to our study. A double-blinded approach would have been ideal, but this was not practical for a number of reasons. Propofol is a white liquid, and the other drugs are all clear liquids. More importantly, the onset times of the drugs are vastly different with propofol having an onset of 1 to 2 min and dexmedetomidine needing to be given slowly by infusion to avoid profound bradycardia so that its neurologic effect is not seen for up to 10 min. The onset of the other drugs is intermediate. Bradycardia, even if not needing treatment, is a physiological "signature" of dexmedetomidine so that even if the solutions were foil wrapped, it would be easy to identify them by their effect.

Our study observed only single sedative administration, and we cannot exclude the possibility that a combination of drugs such as is used in clinical practice may have different effects or magnitude of effects. Our study was performed in a well-defined group of patients with supratentorial brain tumors. We do not know if these results can be extrapolated to patients with other focal lesions such as stroke.

In summary, this prospective, randomized trial in patients with frontal–temporal–parietal brain tumors, the majority of whom had no major neurologic deficit at baseline, found that midazolam and propofol augmented or revealed neurologic dysfunction more frequently than fentanyl and dexmedetomidine when given to the same level of sedation. Patients with high-grade gliomas were more susceptible than those with low-grade gliomas. Therefore, the change in neurologic function has drug specificity and is not a nonspecific sedative effect.

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Competing Interests

The authors declare no competing interests.

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Full protocol available from Dr. Lin: linnan127@gmail.com. Raw data available from Dr. Lin: linnan127@gmail.com.

Correspondence

Address correspondence to Dr. Gelb: Department of Anesthesia and Perioperative Care, University of California San Francisco, 521 Parnassus Avenue, C450, San Francisco, California 94143. adrian.gelb@ucsf.edu. This article may be accessed for personal use at no charge through the Journal Web site, www.anesthesiology.org.

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