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Effect of Cranial Surgery and Brain Tumor Size on Emergence from Anesthesia

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Background: Knowing which neurosurgical patients are at risk for delayed awakening may lead to better utilization of intensive care resources and avoid the risk and cost of pharmacologic reversal and diagnostic tests.

Methods: The authors compared anesthetic emergence from complex spinal surgery (spine; $n = 47$) with that from craniotomy for supratentorial nonfrontal ($n = 22$), frontal ($n = 34$), or posterior fossa tumor ($n = 28$). A further comparison involved patients with small *versus* large (diameter > 30 mm, mass effect) tumors. The standardized anesthetic regimen consisted of induction with 2–4 mg/kg⁻¹ thiopental and 1–2 µg/kg⁻¹ sufentanil, followed by maintenance with nitrous oxide, 0.2–0.5 µg·kg⁻¹·h⁻¹ sufentanil and $\leq 0.5\%$ isoflurane. Sufentanil administration was terminated on dural or spinal muscle closure, isoflurane during skin closure, and nitrous oxide during dressing application. After discontinuing nitrous oxide, a minineurologic examination was performed every 15 min for 1 h, then hourly for 4 h and at 24 h.

Results: Craniotomy patients performed less well than spinal surgery patients on the minineurologic examination 15 and 30 min after discontinuing nitrous oxide. At 15 min, fewer patients with large (*vs.* small) tumors were oriented to time (58% *vs.* 87%; $P < 0.01$) or place (67% *vs.* 90%; $P < 0.01$). Forty-two percent of patients with large tumors still had an abnormal minineurologic examination score *versus* 15% of patients with small tumors. At 30 min, these values were 28% and 8%, respectively ($P < 0.05$). Seventy-one percent of patients with large tumors were oriented to time compared to 97% for small lesions ($P < 0.01$). Emergence from anesthesia was similar for spinal surgery patients and patients with small brain tumors.

Conclusion: Patients undergoing craniotomy for large intracranial mass lesions awaken more slowly than patients after spinal surgery or craniotomy for small brain tumor. (Key

words: Anesthesia: recovery period. Brain: neoplasms. Complications: postoperative. Surgery, spinal: craniotomy.)

IN most instances, rapid emergence from general anesthesia after intracranial neurosurgery is desirable.^{1–3} The most compelling reason for this is the need for the patient to cooperate with a postoperative neurologic examination intended to screen for such potential intracranial disasters as hematoma formation, herniation, and cerebrovascular ischemia. Under these circumstances, residual anesthesia may either give the false impression of a neurologic deficit^{4,5} or prevent the early diagnosis of a developing intracranial problem. Patients who do not awaken promptly after intracranial surgery are frequently subjected to emergency computed tomography and/or cerebral angiography. They also are at greater risk for airway obstruction, hypoxemia, hypercapnia, and aspiration.⁶ In the neurologically compromised patient, such secondary injury can be especially devastating and demands a more intensive level of postoperative care.

Although systematically obtained information about the effect of brain tumor on anesthetic emergence is scant, abnormal cerebral elastance,⁷ frontal lobe pathology, and brain retraction have been implicated as causes for delayed emergence.⁸ Furthermore, it has been the clinical impression of the author and others that large intracranial mass lesions, especially those occurring in the frontal area, can be associated with a longer delay in return to the preoperative mental state.

The ability to predict which patients will awaken more slowly after intracranial surgery is advantageous for clinical management. Decisions concerning the need for continued postoperative tracheal intubation and intensive care resource utilization may be facilitated. Furthermore, the patient may be spared the additional discomfort, risk, and expense associated with various "reversal" regimens, such as the administration of naloxone, physostigmine, or flumazenil. Finally, ad-

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Table 1. Item Checklist for Mini-Neurological Examination

	Score
1. Follows commands	1 (if a or b)
a. Squeezes hand	
b. Sticks out tongue	
2. Verbalization	1
Says "hello" or any correct response below	
3. Orientation	
Gives correct date or weekday	1
Identifies place (institution name/hospital or better)	1
Current U.S. president	1
Names own last or first name	1*
Total	5

*Not scored unless incorrect response to "U.S. president."

ditional postoperative radiologic examinations and associated cost might be avoided.

For these reasons, the investigators set out to study prospectively the time course of anesthetic emergence in patients undergoing craniotomy for removal of brain neoplasms of varying sizes and locations. The principal hypothesis in this study was that craniotomy for removal of large brain tumors is associated with a lower minineurologic score during the first 30 postoperative minutes when compared to craniotomy for small lesions or spinal surgery.

Methods

With institutional approval and patients' written informed consent, the authors studied 131 patients scheduled for elective craniotomy and spinal surgery. An attempt was made to match surgery duration of the control group to that of the craniotomy group by selecting for surgeries expected to last ≥ 3 h. Only patients undergoing partial or complete resection of intracranial tumors were studied whereas those for whom only a biopsy was performed were excluded. We excluded patients who could not answer any component question of a customized minineurologic examination (table 1) preoperatively or if they were taking medications known to affect the minimum alveolar concentration of anesthetics. With the exception of small amounts of sufentanil (5–10 μg intravenous) during placement of invasive monitoring catheters, no other sedative/hypnotic premedicants were given. The anesthetic technique was standardized and consisted

of 2–4 mg/kg^{-1} thiopental and 1–2 $\mu\text{g/kg}^{-1}$ sufentanil for induction, followed by sufentanil infused at a rate of 0.2–0.5 $\mu\text{g/kg}^{-1}/\text{h}^{-1}$, nondepolarizing neuromuscular blockade, nitrous oxide (60%, inspired) and isoflurane ($\leq 0.5\%$, end-tidal), titrated to keep mean arterial pressure within 30% of preoperative values. Before application of the head pins, additional thiopental (1–2 mg/kg^{-1}) was administered. Mechanical ventilation was adjusted to achieve an arterial carbon dioxide partial pressure of 22–28 mmHg. At the time of dural closure for craniotomy patients, and at the time of spinal muscle closure for control subjects, the sufentanil infusion was discontinued. Isoflurane and nitrous oxide were discontinued during skin closure and after application of the head dressing, respectively. Neuromuscular block was reversed with neostigmine and glycopyrrolate. Neither lidocaine nor droperidol was administered before return of patients' mental status to the preoperative state.

Before emergence from anesthesia, the size of the patient's brain lesion was classified as small or large, the location as frontal, nonfrontal supratentorial, or infratentorial. The size of the lesion was categorized on the basis of its appearance on computed tomographic or magnetic resonance imaging scans as small (diameter < 30 mm, no mass effect) or large (diameter ≥ 30 mm, mass effect). Mass effect was defined as midline shift > 3 mm⁹ and the presence of a moderate to large amount of cerebral edema, or the presence of ventricular compression or evidence of compression of the basal cisterns. These characteristics have been previously used by well-known investigators,^{10,11} are associated with a propensity for intracranial pressure elevations,^{9,10} and have been taken as indicators of higher neurologic risk in the perioperative period. The location of brain lesions was indicated as either supratentorial nonfrontal, supratentorial frontal, or infratentorial.

Duration of various surgery phases, dose of anesthetics administered, and end-tidal gas concentrations (by mass spectrometry) were recorded at skin incision, dural incision, dural closure, end of sufentanil infusion, skin closure, application of head dressing, times of discontinuance of isoflurane and nitrous oxide, eye opening, and extubation. Every 15 min after discontinuing nitrous oxide (this event was taken to be the common beginning point from which time to emergence was measured) and at the time of extubation, patients' mental status was assessed in a manner identical to the preoperative examination by recovery room personnel

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Table 2. Characteristics of the Operative Procedure: Spine Surgery and Craniotomy Patients (Mean \pm SD)

	Spine Surgery (n = 47)	Small Tumor (n = 39)	Large Tumor (n = 45)
Duration			
Induction to dressing (h)	5.0 \pm 2.4	5.8 \pm 1.9†	5.7 \pm 1.9†
Opioid off to dressing (min)	50 \pm 25	63 \pm 27†	69 \pm 38‡
Isoflurane off to dressing (min)	10 \pm 11	11 \pm 11	9 \pm 15
N ₂ O off to extubation (min)	6 \pm 4	6 \pm 5	6 \pm 5
Isoflurane off to extubation (min)	19 \pm 11	23 \pm 13	20 \pm 15
Anesthetics			
Isoflurane MAC-hours	1.6 \pm 1.0	2.0 \pm 0.8	1.9 \pm 0.8
Total sufentanil dose (μ g/kg)	2.1 \pm 0.9	2.2 \pm 1.0	2.4 \pm 0.7
Total thiopental dose (mg/kg)	3.4 \pm 1.5	3.9 \pm 1.4	3.9 \pm 1.2
PETIso (when discontinued)	0.22 \pm 0.11	0.24 \pm 0.9	0.26 \pm .12
PETIso (when N ₂ O discontinued)	0.06 \pm 0.09	0.08 \pm 0.08	0.07 \pm 0.09
Miscellaneous			
PETCO ₂ (at dural closure*)	26 \pm 3	23 \pm 4‡	22.0 \pm 3‡
Temperature (at closure, °C)	35.5 \pm 0.7	35.9 \pm 0.8†	35.9 \pm 1.0

*At skin closure for spine surgery group.

† $P < 0.05$ versus spine surgery.‡ $P < 0.01$ versus spine surgery.

who were unaware of the size classification of the brain tumor. This assessment was continued every 15 min for 1 h, then every hour for 4 h and at 24 h. In addition, serum electrolytes, blood urea nitrogen, blood glucose, and arterial blood gas analysis were obtained during the first 2 h postoperatively in the majority of patients. The use of major radiologic diagnostic tests such as lateral skull film, and computed tomographic and magnetic resonance imaging scans, within the first 24 h postoperatively was also noted. The frequency of utilization and cost to the patient of these radiologic diagnostic tests were calculated and related to the occurrence of delayed emergence at 15 and 30 min postoperatively. Blood samples were obtained at 30 and 120 min after discontinuation of nitrous oxide for determination of plasma sufentanil concentrations. The plasma was separated and frozen until analyzed by radioimmunoassay as previously described.¹² The reagents for this assay were obtained from Janssen Lifesciences Products (Piscataway, NJ). Plasma concentrations that were reported as below the threshold of detection for the assay (<0.05 or <0.1 ng/ml⁻¹) were arbitrarily assigned a value of 0.05 ng/ml⁻¹ to facilitate statistical analysis.

Statistical Analysis

Baseline and Intraoperative Comparisons. Descriptive statistics were calculated for demographic

variables, anesthetic doses, and characteristics of the time course of the anesthetic procedure. Patients were compared on these factors by study group (tumor *vs.* spine), by tumor size (spine *vs.* small tumor *vs.* large tumor), and within the tumor group by location.

Univariate Emergence Analysis. Outcomes of primary interest were delayed emergence on the minineurologic examination (≤ 4), the ability to follow commands and orientation to time and place (yes/no), assessed at 15 and 30 min. Baseline and intraoperative variables, study group, tumor size, tumor location, and tumor size by location were assessed for significant association with each outcome.

Statistical Tests. Groups were compared on continuous variables with a two-tailed *t* test, an analysis of variance, or their nonparametric counterparts, and on categorical variables with a chi-square test or Fisher's exact test. Logistic regression was used to assess the size by location interaction.

Multivariable Emergence Analysis. Stepwise logistic regression with a $P < 0.05$ criterion was performed to find the combination of factors that, taken together, best explain delayed emergence, as defined by a minineurologic examination score ≤ 4 at 15 and 30 min postoperatively. Study group (spine, small tumor, large tumor) and all other baseline and operative factors were considered in the models.

For all hypotheses, a significance criterion of 0.01 was

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Table 3. Percent of Spine and Craniotomy Patients Who Failed to Achieve Emergence Criteria

	Spine (n = 47)	Small Tumor (n = 39)	Large Tumor (n = 45)
At 15 min			
Mini-neurological examination <5	8.5	15.4	41.5*
Does not follow command	0	0	8.9*
Not oriented to time	8.5	12.8	42.2*
Not oriented to place	4.3	10.3	33.3*
At 30 min			
Mini-neurological examination <5	4.3	7.7	27.9†
Does not follow command	0	0	4.4
Not oriented to time	4.3	2.6	28.9*
Not oriented to place	4.3	5.1	17.8

* $P < 0.01$ versus spine and small tumor.† $P < 0.01$ versus spine.

fewer tumor patients were oriented to time and place ($P < 0.01$; fig. 2). All spinal surgery patients could follow commands, whereas 2.4% of tumor patients could not. More tumor than spinal surgery patients had a minineurologic score of less than five (28.8% vs. 8.5%, respectively; $P < 0.01$). Thirty minutes after termination of nitrous oxide, 16.7% of tumor patients were still disoriented as to time versus 4.3% of control subjects ($P < 0.05$). More tumor than spinal surgery patients had a minineurologic score lower than five (18.3% vs. 4.3%, respectively; $P < 0.05$). Further analysis separately comparing small and large tumors to the spinal surgery group indicates that the differences in emergence between tumor and spinal surgery patients are predominantly owing to tumor size (see below and table 3).

Postoperative serum sodium, potassium, and chloride concentrations were within the normal ranges and did not differ between the spinal surgery and craniotomy groups. The same was true for arterial pH level, carbon dioxide tension, and blood urea nitrogen concentration. Blood glucose level (196 ± 49 vs. 155 ± 57 mg/dl) and hemoglobin oxygen saturation (98 ± 2 vs. $96 \pm 2\%$) were higher in the craniotomy group. However, neither factor significantly impacted emergence outcomes.

The frequency with which postoperative radiologic tests (skull radiograph, computed tomographic and magnetic resonance imaging scans, and cerebral angiogram) were obtained, was not significantly associated

with delayed emergence (orientation to time) at 15 or 30 min. Fifty-eight percent (35 of 60) of patients who were appropriately oriented to time 15 min postoperatively required computed tomographic or magnetic resonance imaging scans of the head within 24 h of the conclusion of surgery, compared with 67% (14 of 21) in patients who were not oriented. At 30 min, the corresponding frequencies were 61% (42 of 69) and 58% (7 of 12), respectively. Total radiologic diagnostic cost during the 24 h after surgery was $\$636 \pm 422$ in patients whose emergence (orientation to time) was delayed at 15 min and $\$544 \pm 428$ in patients who were appropriately oriented at this time ($P = 0.36$). For delayed vs. appropriate emergence at 30 min, the radiologic costs were $\$574 \pm 438$ and $\$531 \pm 366$, respectively ($P = 0.81$). Owing to the sample size and the large standard deviations observed, there was only sufficient statistical power to detect differences in cost of \$300 or more.

Effect of Tumor Size

Patient age, gender, weight, and comorbid hypertension or cardiac disease were similar in the small and large tumor groups, as were the characteristics of the operative procedure (table 2). Significantly more patients with large than small tumors had a minineurologic score less than 5 and fewer patients with large tumors were oriented to time and place at 15 min than were patients with small lesions (table 3). Even at 30 min, this difference was significant for the minineurologic score and orientation to time.

Plasma Sufentanil Concentrations. Postoperative plasma sufentanil concentrations were available in 49 of 84 tumor patients and in 24 of 47 control subjects. Thirty and 120 min postoperatively, plasma sufentanil concentrations were 0.23 ± 0.13 and 0.16 ± 0.11 ng/ml, respectively in tumor patients and 0.23 ± 0.13 and 0.17 ± 0.12 ng/ml, respectively in spinal surgery patients. At 120 min, plasma sufentanil concentration was statistically different from the concentration at 30 min in the tumor ($P < 0.001$) and in the spinal surgery ($P = 0.03$) groups. Plasma sufentanil concentration was neither associated with delayed emergence nor with type of intracranial neurosurgery. For the purposes of the analyses involving plasma sufentanil concentrations, delayed emergence was defined as the frequency of failure to be oriented to time.

Multivariable Analysis. At 15 min postoperatively, the logistic regression model for association with delayed emergence (minineurologic score ≤ 4) included

time from discontinuation of isoflurane to extubation, in addition to study group. Taking this additional variable into account, the odds (95% confidence interval) of delayed emergence were 8.2 (2.3-28.7) times that for patients with large tumors than for spinal surgery patients and 4.9 (1.6-15.5) times greater for patients with large tumors than for those with small tumors. At 30 min, the additional variable in the logistic regression model was the end-tidal concentration of isoflurane (P_{ET-Iso}) when nitrous oxide was discontinued. The odds of delayed emergence were 8.7 (1.8-41.7) times greater for large tumor than spinal surgery patients and 4.6 (1.2-18.0) times higher for patients with large tumors than for those with small tumors. Location of brain tumor was not a factor significantly affecting delayed emergence and was therefore not included in the model for either time. Results from the multivariate model therefore corroborated our conclusions about the effect of tumor size on emergence.

Discussion

Our data provide information regarding the influence of intracranial pathology on the emergence characteristics of patients undergoing brain tumor resection. To date, such information has not been reported systematically. When compared to noncranial surgery, craniotomy for tumor excision was associated with prolonged return to preoperative mental status. Surgery for removal of larger brain tumors was associated with a higher incidence of delayed emergence in the early postoperative (*i.e.*, ≤ 30 min) period when compared to surgery for smaller tumors or noncranial neurosurgery.

Emergence after anesthesia is a process characterized by large individual variability. No universally accepted criteria for the definition of prolonged emergence exist. However, difficulty with arousal beyond 15 min after the cessation of anesthesia has previously been assumed to constitute prolonged emergence.¹³⁻¹⁵ Reported mean times to orientation and awakening after anesthesia for craniotomy depend somewhat on the anesthetic regimen, but range from 8 to 61 min.^{3,16,18,19}

|| Ravussin P, Berger-Bayer M, Nydegger M, Freeman J: Thiopental-isoflurane vs. propofol in neuroanesthesia for intracranial surgery. (Abstract) *Anesthesiology* 1988;69:A577.

Merckx L, Van Hemelrijck J, Van Aken H, Plets C, Goffin J: Total intravenous anesthesia using propofol and alfentanil infusion in neurosurgical patients. (Abstract) *Anesthesiology* 1988;69:A576.

Zelcer and Wells¹⁵ found a 9% incidence of unresponsiveness 15 min after general anesthesia among 443 recovery room patients. The clinician's definition of delayed emergence may vary with the specific clinical situation. After intracranial neurosurgery, the operative team is usually intent on obtaining a neurologic assessment of the patient as soon as possible, so that a 15-30-min period of obtundation is the maximum tolerable before an intervention is contemplated. For this reason, the authors chose to concentrate their observations in the early postoperative period.

Our choice of postoperative neurologic testing was influenced by practical considerations as well as by previous definitions of postoperative delirium. We intended to concentrate on components of the neurologic and mental status examination that would be expected to be useful during the immediate postoperative evaluation of the craniotomy patient. Others have emphasized that disorientation is a *sine qua non* for the diagnosis of postoperative delirium, but also describe concomitant attention, thought process, perception, and memory deficits.¹⁷ Disorientation to time appears to be the most vulnerable component of orientation.¹⁷ Our results, especially those shown in figure 1, also indicate that disorientation to time was the most pervasively affected emergence parameter after craniotomy for brain tumor.

The most prevalent cause of prolonged awakening from anesthesia is assumed to be drug or anesthetic effect.¹⁴ Inhalational¹⁸ and intravenous anesthetics,¹⁹ anesthetic adjuncts,²⁰ premedicants,²¹ and agents potentiating these drugs have all been implicated in delayed arousal.²² It has even been suggested that opioids, particularly sufentanil, are associated with exacerbation of postinjury neurologic deficits,^{4,5,23} which include failure to regain preoperative mental status.

The standardized anesthetic regimen employed in the current investigation was intended to control for influences of anesthetic type and dose on emergence. Nevertheless, because anesthesiologists could not be blinded to the surgery, individual practice patterns may have introduced certain biases. It is thus conceivable that patients were treated differently according to attributes thought to influence the speed of awakening. Such systematic bias may have occurred in the management of our spinal surgery patients, considering their shorter observed time from discontinuance of the opioid infusion to the end of the surgery, when compared to brain tumor patients. Fortunately, the direction of this particular bias did not affect our ability to conclude

that tumor patients may independently are age, language, electrolyte disturbance.^{14,24-26} Our groups with regular electrolyte levels and heavier than likely owing to emergence. The by the evaluation the two groups. characteristics with emergence. Longer duration recovery.^{14,27} not identical in for tumor excision patients. Tumors were, on average cases, which require minimum alveolar groups' mean postoperative were nearly identical is unlikely that, 40 min would emergence delay (5.7 \pm 1.8 vs. 5.7 \pm 1.8) alveolar concentrations were extremely tumor groups, emergence characteristics hourly dose of isoflurane at the end of the anesthetic and the plasma after termination the craniotomy for potential complications, we accounted for the time from extubation and the continued in the logistic relationship emergence was patients had the than craniotomy together with the surgery at the end of surgery longer emergence

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that tumor patients emerged more slowly. Factors that may independently affect emergence from anesthesia are age, language difficulties, metabolic abnormalities, electrolyte disturbances, epilepsy, and covert drug abuse.^{14,24-26} Our data show no differences between groups with regard to age, prevalence of seizures, or electrolyte levels. Although control patients were taller and heavier than tumor patients, this difference was likely owing to gender, a factor not known to alter emergence. The incidence of obesity, as determined by the evaluating anesthesiologist, was not different in the two groups. In any event, neither of these biologic characteristics was found to be statistically associated with emergence delay.

Longer duration of anesthesia can lead to prolonged recovery.^{13,14,27} Duration of anesthesia was similar but not identical in patients who underwent craniotomy for tumor excision, when compared to spinal surgery patients. Tumor patients had procedure times which were, on average, 40 min longer than spinal surgery cases, which resulted in marginally greater isoflurane minimum alveolar concentration hours. However, both groups' mean procedure times were at least 5 h; the postoperative plasma concentrations of sufentanil were nearly identical in tumor and control patients. It is unlikely that, after 5 h of anesthesia, an additional 40 min would have resulted in a clinically important emergence delay. Furthermore, procedure duration (5.7 ± 1.8 vs. 5.7 ± 1.9 h) and isoflurane minimum alveolar concentration hours (1.9 ± 0.8 vs. 1.9 ± 0.8) were extremely well matched in the large and small tumor groups, despite their decidedly different emergence characteristics. Our data also show that the total hourly dose of sufentanil, the end-tidal concentration of isoflurane at the end of administration of the anesthetic and the plasma sufentanil concentration 30 min after termination of nitrous oxide were equivalent in the craniotomy and control groups (table 2). To adjust for potential confounders stemming from the anesthetic, we accounted for two univariately significant factors, the time from discontinuation of isoflurane to extubation and the $P_{ET}Iso$ when nitrous oxide was discontinued in the logistic regression models. In doing so, the relationship between brain tumor size and delayed emergence was just as strong. Furthermore, control patients had the sufentanil infusion discontinued later than craniotomy patients, which should have—together with the slightly colder state of control patients at the end of surgery—further biased our study toward longer emergence times in this group.

Hyperventilation changes human sufentanil pharmacokinetics, resulting in a higher total volume of distribution and longer elimination half-life.²⁸ Similarly, brain concentration of fentanyl was increased in hyperventilated dogs,²⁹ presumably because of reduced brain washout and a change in the drug lipid/plasma distribution coefficient caused by the higher pH level. Higher brain opioid concentrations could slow emergence from anesthesia. The slower awakening of our craniotomy patients, who were also aggressively hyperventilated, therefore, could theoretically have been related to altered sufentanil pharmacokinetics. Intraoperative hypocapnia has previously been linked to postoperative impairment in reaction time and short-term memory.²⁰ Although end-tidal partial pressure of carbon dioxide was significantly lower in the tumor group during the early part of the surgical procedure, the difference was small (average of 3.5 mmHg). Furthermore, end-tidal partial pressure of carbon dioxide was similar to the control group by the time of surgical closure. Most importantly, despite their more prominent emergence delays, patients with large tumors were hyperventilated in a manner identical to patients with small tumors. On balance it therefore seems unlikely that hypocapnia played a role in accounting for the delays in emergence of craniotomy patients. Given these observations, we cannot attribute the observed differences in emergence to differences in the anesthetic regimen. Rather, we suggest that the surgical trespass on the brain, particularly with larger lesions, is an independently operative factor.

It is possible that our conclusions could potentially have been affected by a change in surgical practice during the 5-yr study period. Our neuroanesthetic and neurosurgical practices have remained relatively stable during the entire study period. The majority of neuroanesthesiologists who practiced at the beginning of the study did so at the end. Surgical practice has gradually but increasingly used stereotactic guidance. It is estimated that approximately 40–50% of craniotomies were performed with stereotactic guidance at the outset of the study and about 70% at its conclusion. Toward the end of the enrollment period fewer craniotomies for metastatic tumor were performed because of an increasing trend toward radiotherapeutic intervention. These trends are mentioned for completeness but their significance with respect to our results is unclear. We believe that they do not affect the conclusions of our study, because the preliminary findings

gathered from the first 60% of our patients are corroborated by the remainder of the study enrollees.

Little has been written about the influence of intracranial disease on the quality of emergence from anesthesia. When Losasso *et al.*⁵⁰ compared cervical spinal surgery with craniectomy in a study assessing the effects of nitrous oxide on venous air embolism risk, they found that emergence times were slightly longer for craniotomy patients. They attributed this difference to the degree of brain exposure in the operative field, but could not rule out the influence of such other variables as length of surgery and anesthetic exposure. Todd *et al.*¹⁶ observed that patients with midline intracranial tumors required a longer time to become oriented after craniotomy. Although a relationship between tumor volume and emergence characteristics was not evident, their study was not specifically designed to tests this hypothesis, lacking statistical power. Conventional teaching has held that certain conditions may predispose to slow awakening. These include a depressed preoperative mental state such as, for example, is seen in patients with cerebral palsy,^{17,24,31} psychiatric disease,^{14,26} extensive surgical dissection, occurrence of brain stem ischemia, severe pneumocephalus,³² seizures,⁷ and surgical trespass in the area of the frontal lobes.

If one accepts the notion that emergence after brain surgery can be independent of anesthetic factors, the question of a potential mechanism is an interesting one. Brain tissue shifts have been reported to associate with depression of consciousness.¹¹ Among these, horizontal shifts were most directly related to level of consciousness. One might postulate that surgical intervention, brain tissue dehydration and hyperventilation could occasion a relative shift in brain tissues during the immediate postoperative period. Compression or traction on such structures as the brain stem or the thalamic reticular activating system may explain the effect of brain shifts on depression of consciousness.¹¹ In support of the latter goes our observation that larger brain tumors predisposed to slower return of preoperative mental state. It is conceivable that subtle brain shifts occur particularly where a large amount of tissue is removed surgically. Alternatively, one may speculate that the greater amount of brain edema associated with large brain tumors may lead to a slower washout of anesthetic agents. Despite these considerations, it must also be understood that small strategically placed lesions could lead to depression in consciousness postop-

eratively, such as ischemia or compression in the territory of the reticular activating system.

The analysis of early postoperative radiologic diagnostic costs indicates that delayed emergence did not result in a significantly higher or "panic" ordering of expensive neuroradiologic procedures during the first postoperative day. It may merely indicate that the surgeons at our hospital expect a certain degree of somnolence for at least 30 min postoperatively that does not require urgent additional diagnostic studies. It is still possible that more tests were ordered earlier within the 24-h time period in patients with delayed return of orientation, an issue that was not addressed in this study. However, by 24 h, cumulative radiologic cost no longer depended on immediate postoperative neurologic status. Further information needs to be gathered to inform clinicians of a safe time interval that can be allowed before diagnostic intervention becomes necessary in the somnolent postcraniotomy patient.

In this study, patients undergoing craniotomy for removal of brain tumor were slower to emerge from anesthesia than a group of neurosurgical patients undergoing spinal surgery. Patients with large intracranial tumors (>30 mm diameter, mass effect) predominantly accounted for this difference. The cranial radiologic diagnostic cost during the first postoperative day was not significantly greater in patients with slower emergence patterns. We conclude that emergence from anesthesia after craniotomy for large tumor masses is delayed during the first 30 postoperative minutes when compared to noncranial neurosurgery or craniotomy for small tumors.

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References

1. Black S: Cerebral aneurysm and arteriovenous malformation. Clinical Neuroanesthesia. Edited by Cucchiara RF, Michenfelder JD. New York, Churchill-Livingstone, 1990, pp 223-54
2. Cucchiara RF, Black S: Tumor surgery. Clinical Neuroanesthesia. Edited by Cucchiara RF, Michenfelder JD. New York, Churchill-Livingstone, 1990, pp 285-308
3. From RP, Warner DS, Todd MM, Sokoll MD: Anesthesia for craniotomy: a double-blind comparison of alfentanil, fentanyl, and sufentanil. ANESTHESIOLOGY 1990; 73:896-904
4. Benzel EC, Hadden TA, Nossaman BD, Lancon J, Kesterson L:

Does sufentanil exac-
rosurg Anes 1990; 2
5. Krechel SW, C
Naloxone: Report of
1:346-51
6. Parr SM, Robin
sciousness on arriva
early respiratory mo
7. Mahla ME: Ne
Anesthesia. Edited
1991, pp 394-419
8. Amyes RW, Ni
lesions of the anteri
1955; 20:117-30
9. Grosslight K, I
neuroanesthesia: Ri
ANESTHESIOLOGY 198
10. Bedford RF, M
surgery for supraten
puted tomography s
11. Roppa AH:
consciousness in pa
Med 1986; 3:4:953
12. Michien M, I
the new opiate anal
macokinetic profile
13. Apfelbaum JL
Roizen MF, Stanley T
clinical experience c
propofol: characteri
ing. Anesth Analg 19
14. Crosby G: Cer
ative period. Causes
ogy 1992; 20:53-68
15. Zelcer, Well
cations. Anesth Int
16. Todd MM, W
Scamman FL: Kirchs
anesthetics for elec
1993; 78:1005-20
17. Lipowski ZJ:
sion. J Nerv Ment D