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Emergence Patterns from General Anesthesia after Epilepsy Surgery: An Observational Pilot Study

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Abstract

Objective Emergence from anesthesia starts from the limbic structures and then spreads outwards to brainstem, reticular activating systems, and then to the cortex. Epilepsy surgery often involves resection of limbic structures and hence may disrupt the pattern of emergence. The aim of this study was to explore the pattern of emergence from anesthesia following epilepsy surgery and to determine associated variables affecting the emergence pattern.

Setting and Design Tertiary care center, prospective observational study.

Materials and Methods We conducted a prospective observation pilot study on adult patients undergoing anterior temporal lobectomy and amygdalohippocampectomy for epilepsy. Anesthesia management was standardized in all patients, and they were allowed to wake up with "no touch" technique. Primary outcome of the study was the pattern of emergence (normal emergence, agitated emergence, or slow emergence) from anesthesia. Secondary outcomes were to explore the differences in preoperative neuropsychological profile and limbic structure volumes between the different patterns of emergence. Quantitative variables were analyzed using Student's *t*-test. Qualitative variables were analyzed using chi-square test.

Results Twenty-nine patients completed the study: 9 patients (31%) had agitated emergence, and 20 patients had normal emergence. Among the agitated emergence, 2 patients had Riker scale of 7 indicating violent emergence. Patient demographics, anesthetic used, neuropsychological profile, and limbic structure volumes were similar between normal emergence and agitated emergence groups. However, two patients who had severe agitation (Riker scale of 7) had the lowest intelligence quotient.

Keywords
- epilepsy surgery
- emergence
- agitation
- anesthesia

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Conclusion Our pilot study showed that emergence agitation is not uncommon in patients undergoing epilepsy surgery. However, due to smaller sample size, the role of preoperative neuropsychologic profile and hippocampal volumes in predicting the pattern of emergence is inconclusive.

Introduction

Smooth and rapid emergence (wake-up) following surgery is a crucial part of the anesthetic management of patients undergoing neurosurgical procedures. Physiologically, emerging from deep anesthesia usually involves a fixed pattern with several phases.[1] These include rapid autonomic arousal, a slow return of brainstem reflexes, followed by reflexive or uncoordinated movements, and finally the response to simple commands. Interestingly, emergence from anesthesia starts with the activation of deep brain structures, namely, subcortical and limbic regions.[1,2] Later, these become functionally coupled with other parts of the brain including the frontal and inferior parietal cortex. Arousal (spoken command)-induced brain activations during emergence from anesthesia are mostly localized in deep, phylogenetically old brain structures (hippocampus or limbic cortex or mesial temporal structures) than in neocortex.[1,3] Thus, the emergence of a conscious state precedes the full recovery of neocortical processing required for establishing contact with the surroundings.[2] Brain surgeries, especially, epilepsy surgery may interfere with these structures directly or indirectly.

Epilepsy surgery is indicated in patients with medically refractory seizures.[4] Anterior temporal lobectomy (ATL) and amygdalohippocampectomy (AH) is a well-established surgical treatment for patients with temporal lobe epilepsy (TLE).[4] In TLE, there is a pathological alteration of limbic and mesial temporal structures.[5] In addition, there is an asymmetry (dominant vs. nondominant) of temporal neocortical and mesial functional representations in patients with TLE.[5] In theory, loss of these structures can lead to modification of the emergence pattern from general anesthesia (GA). Therefore, the aim of this prospective observational pilot study was to explore the pattern of emergence from anesthesia following ATL and AH, and to determine associated variables affecting the emergence pattern.

Material and Methods

This prospective, observational pilot study was conducted after the approval from the institutional research ethics board and written informed consent was obtained from each subject. Consecutive patients (age $>$ 18 years) scheduled for elective ATL and AH under GA during a 2-year period (2015–2017) were recruited for this study. Patients who refused to provide consent, or those who needed planned or unplanned postoperative intensive care unit admission were excluded.

Anesthesia Management

The standard preoperative preparation of the patient for ATL and AH was undertaken as per our institutional practice. All patients had Canadian Anaesthesia Society standard monitoring consisting of a 5-lead electrocardiogram, non-invasive blood pressure, oxygen saturation, end-tidal carbon-dioxide levels, and end-tidal anesthetic agent concentration. In addition, the depth of anesthesia was monitored using Entropy (Datex-Ohmeda Inc., GE Healthcare, Helsinki, Finland). Anesthesia was induced with propofol (1–2 mg/kg), fentanyl (2–3 mcg/kg), and rocuronium (0.8–1.2 mg/kg). Anesthesia was maintained with oxygen, air, sevoflurane (0.8–1 age-adjusted minimal alveolar concentration [MAC]), and remifentanil infusion titrated to keep entropy within 45 to 55. After the induction and positioning, the surgery (ATL and AH) proceeded as per the standard protocol. After the dural closure, inhalational agent concentration was gradually decreased to MAC of 0.6, and fentanyl 1 to 2 mcg/kg was administered for the additional analgesia. After the closure of the scalp, the inhalational agent was turned off and the gas flow rates were increased to 10 L/min. Neostigmine (2.5 mg) and glycopyrrolate (0.4 mg) were given to reverse the neuromuscular blockade. Remifentanil infusion was turned off once the head was disengaged from the head pins and after the completion of the head dressing. The patients were allowed to wake up with "no touch technique." The tracheal extubation was performed when the patients were breathing adequately, spontaneously, and obeying commands. Postsurgery, all patients were recovered in the postanesthesia care unit (PACU) before being discharged to the neurosurgical critical care unit.

Surgical Management

Under frameless stereotaxy and a standard frontotemporal incision, ATL was done with the medial border of resection as the lateral border of the ventricles and to the anterior tip of the middle temporal fossa. This is followed by the resection of the amygdala and hippocampus and parahippocampal gyrus.

Data Collection

The data was collected from the time of turning off the anesthetic agent till the transfer from the PACU. Data collected included patient demographics, age at seizure onset, preoperative neuropsychological assessments (intelligence quotient [IQ], verbal and nonverbal memory, language dominance, dexterity of the patient, education, and history of psychiatric illness), side of the surgery, time of emergence from anesthesia, vital signs, and Glasgow Coma Scale (GCS)

score. Quality of emergence was assessed using a Riker agitation score (7, agitated: dangerous agitation; 6, very agitated; 5, agitated; 4, nonagitated: calm and cooperative; 3, sedated but arousable; 2, very sedated; 1, unarousable).[6] Patients were assessed every 5 minutes for the first 30 minutes, and every 10 minutes for the next 60 minutes. In addition, volumetric analysis of bilateral amygdala hippocampus and thalamus were done from the T1 sequence of magnetic resonance imaging brain and represented as a volume in mm^3.

Outcome Measures

The primary outcome of the study was the pattern of emergence from GA. Emergence characteristics were classified as either normal emergence (Riker scale = 4), agitated emergence (Riker scale > 4), or slow emergence (Riker scale < 4). Secondary outcomes were to explore the differences in preoperative neuropsychological profile and limbic structure volumes between the different patterns of emergence.

Data Analysis

No prior sample size calculation was performed. A minimum of 30 patients were targeted to achieve a minimum sample size for the pilot study. Descriptive statistics (frequency) were used to state normal or abnormal emergence patterns and volumes of limbic structures (amygdala, hippocampus, and thalamus). Quantitative variables were analyzed using Student's *t*-test. Qualitative variables were analyzed using the chi-square test. A *p*-value less than 0.05 was considered significant.

Results

In total, 36 patients were recruited, and 7 patients were excluded for missing data (►**Fig. 1**). Data from 29 patients were included in the final analysis. The mean (± standard deviation) age was 34.5 (12) years, and 13 (45%) patients were female. The demographic variables of the study subjects are shown in ►**Table 1**.

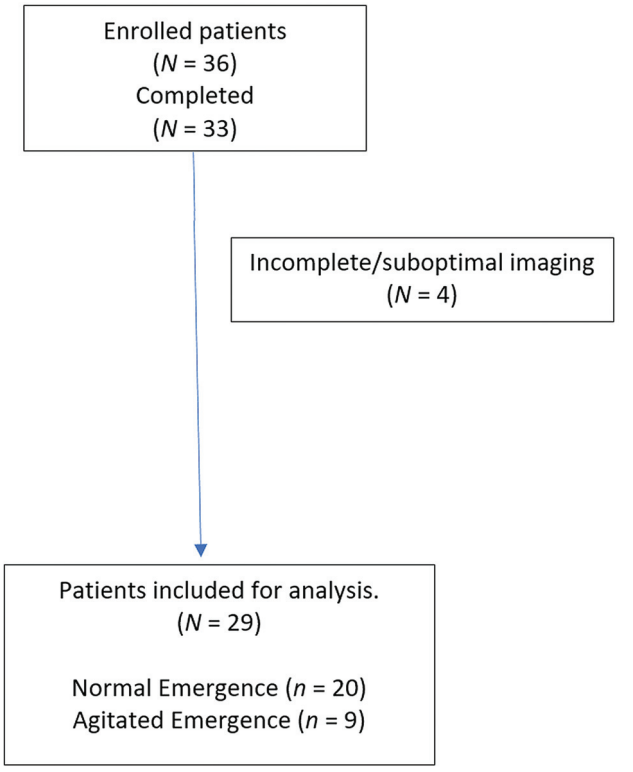

Fig. 1 Study flowchart. *N*, number.

Out of 29 patients, 20 had normal emergence and 9 patients exhibited agitated emergence. There were no patients with slow emergence. Among nine patients with agitated emergence, two patients showed severe agitation (Riker scale 7). Emergence agitation was treated with either propofol boluses and/or dexmedetomidine bolus followed by infusions.

There was no statistically significant difference between the two groups in terms of demographics, duration of surgery, time to achieve a GCS score of 15, and intraoperative utilization of anesthetics and opioids. Similarly, both groups

Table 1 Demographic variables and anesthetic agent use

	Normal emergence ($n = 20$)	Agitated emergence ($n = 9$)	*p*-Value
Age (y)	36 ± 13	33 ± 11	0.54
Female gender, *n* (%)	9 (45%)	4 (44%)	0.32
Weight (kg)	75 ± 19	76 ± 15	0.83
Height (cm)	170 ± 9	174 ± 10	0.32
Duration of surgery (min)	240 ± 29	252 ± 37	0.40
Time from stopping anesthetic agent to GCS score 15 (min)	11 ± 3	12 ± 2	0.59
Total fentanyl used (μg)	211 ± 37	216 ± 43	0.75
Total propofol used (mg)	296 ± 112	330 ± 78	0.34
End-tidal sevoflurane concentration (%)	0.94 ± 0.17	0.96 ± 0.14	0.82
Total remifentanil used (μg/kg/min)	0.07 ± 0.05	0.05 ± 0.04	0.74

Abbreviation: GCS, Glasgow Coma Scale.

Table 2 Neuropsychologic profile

	Normal emergence ($n = 20$)	Agitated emergence ($n = 9$)	*p*-Value
Dominance (right:left)	13:7	8:1	0.18
Age at seizure onset (y)	23 ± 16	22 ± 12	0.82
Verbal IQ	97 ± 11	98 ± 12	0.81
Visuospatial IQ	92 ± 12	91 ± 13	0.93
Total IQ	93 ± 10	94 ± 11	0.84
Psychiatric illness present	2 (10%)	2 (22%)	0.57
Education (postsecondary completed)	13 (65%)	7 (77%)	0.36

Abbreviation: IQ, intelligent quotient.

Table 3 Ipsilateral and contralateral hippocampus, amygdala, and thalamic volumes

Volumes	Normal emergence	Agitated emergence	*p*-Value
Ipsilateral hippocampus (mm^3)	$3{,}903 \pm 516$	$3{,}578 \pm 344$	0.73
Ipsilateral amygdala (mm^3)	$1{,}295 \pm 285$	$1{,}331 \pm 272$	0.81
Ipsilateral thalamus (mm^3)	$7{,}479 \pm 856$	$7{,}311 \pm 663$	0.74
Ipsilateral A + H (mm^3)	$4{,}842 \pm 687$	$4{,}737 \pm 644$	0.82
Ipsilateral A + H + thalamus (mm^3)	$12{,}324 \pm 1{,}320$	$12{,}286 \pm 1{,}245$	0.56
Contralateral hippocampus (mm^3)	$3{,}525 \pm 569$	$3{,}479 \pm 452$	0.68
Contralateral amygdala (mm^3)	$1{,}260 \pm 230$	$1{,}321 \pm 223$	0.74
Contralateral thalamus (mm^3)	$7{,}631 \pm 799$	$7{,}608 \pm 908$	0.83
Contralateral A + H (mm^3)	$5{,}143 \pm 691$	$4{,}972 \pm 421$	0.66
Contralateral A + H + thalamus (mm^3)	$12{,}771 \pm 1{,}376$	$12{,}343 \pm 1{,}030$	0.74

Abbreviations: A, amygdala; H, hippocampus.

were also comparable with regard to their preoperative neuropsychological assessments (IQ, educational [post-secondary], history of psychiatric illness) (►**Table 2**). However, two patients who had severe agitation (Riker scale of 7) had the lowest IQ (85). Age at the seizure onset was also similar between the groups; however, 88.9% of patients in agitated emergence were right-handed when compared to 65% in the normal emergence group.

With regards to volumetric analysis, the volumes of the hippocampus, thalamus, and amygdala in both ipsilateral and contralateral sides, respectively, in both groups were similar (►**Table 3**). However, patients with agitated emergence had on average 400 mm^3 smaller contralateral limbic structure (amygdala, hippocampus, and thalamus) volume than patients with normal emergence. This was not statistically significant.

Discussion

This prospective observational pilot study of 29 patients undergoing ATL and AH for refractory epilepsy show that agitated emergence is not uncommon and represents one-third of patients in this pilot study. Smooth and rapid emergence (wake-up) following surgery is a crucial part of the anesthetic management of patients undergoing neurosurgical procedures. This is because large swings in blood pressure during abrupt and stormy emergence may cause intracranial hemorrhage and an increase in brain swelling. In addition, postanesthesia agitation can cause several adverse consequences including the development of early or late delirium and related complications, higher pain scores, and respiratory complications.[7] On the other hand, slow and delayed recovery jeopardizes timely neurological assessment. Therefore, it is imperative to understand the link between, the pattern of emergence and its relationship with the loss of brain structures.

Traditionally, the induction of GA has been an active and rapid process while emergence, by contrast, is considered a passive process that varies in length and may be defined by different neural trajectories of recovery,[8] although this assumed passivity has been questioned.[9,10] In this study, none of the patients had slow emergence, though one-third had agitated emergence. This implies that the pathway that regulates the quality of emergence may be different from, and cannot be fully explained by, the traditional mechanisms thought to cause delayed emergence.

The pattern of emergence from smooth to agitation could be multifactorial including types of anesthesia, surgical factors, pain, and preoperative neuropsychological status.[7] In our series, both groups showed similar characteristics for

the above-mentioned factors. Though there was a small difference in the mean propofol dose between the groups, but this was not statistically significant. Higher dose of propofol in the agitated group may be due to additional propofol needed during emergence due to agitation. The role of different types of anesthetics is still controversial. In a recent review, the time to emergence from anesthesia in patients undergoing brain tumor surgery was not different with inhalational anesthesia (sevoflurane) compared with intravenous anesthesia (propofol).[11] In our study patients had a similar time reaching GCS score of 15 in both groups, with similar anesthetics use, and comparable opioid consumption. This demonstrates that the pattern of emergence may be differently modulated despite the similar time to emergence, underscoring the underlying differential mechanism.

Neuropsychological testing is an integral part of the evaluation when considering epilepsy surgery.[12] Presurgical neuropsychological testing predicts cognitive and seizure outcomes after ATL. Preoperative neuropsychological assessment quantifies the expected loss of higher mental functions in these patients and may help predict long-term postoperative behavior changes. The components of neuropsychological assessment which can have a cause-effect relationship with abnormal postanesthetic emergence include age, education, IQ, language dominance, memory (verbal-visual) lateralization, and the history of psychiatric illness.[12,13] On a theoretical level, neuropsychological findings fit with the hypothesis that greater brain reserve capacity (e.g., as reflected in a higher intelligence, higher educational level, or larger overall brain volume) serves as a protective factor in the face of brain insults.[14,15] Applied to the present study, this theory would suggest that patients with greater cognitive skills within the verbal or nonverbal domains before surgery have a better chance of normal emergence in the immediate postoperative period. Though we were not able to prove a correlation between the neuropsychologic profile and the emergence patterns in our study, we did notice that two patients with the lowest IQ had the most severe agitation. Furthermore, in general, patients with poor preoperative neuropsychological functions are usually not surgical candidate.

Anatomical and functional variations of the hippocampus have been shown to play a role in sleep dysfunction, altered emergence from anesthesia, or undermined learning and memory.[16–18] Similarly, reduced amygdala volume is associated with deficits in inhibitory control.[19] Theoretically, it is plausible that larger volume may be a marker for better protection against agitated emergence, in consonance with the theory that a better brain reserve capacity would help for smoother emergence after anesthesia. Our agitation emergence group showed smaller (not statistically different) contralateral limbic volume compared to the normal emergence group. Though, given lack of significance as well as the small sample size, we cannot emphasize this finding concretely. But, at least in theory, this finding may be in line with "the theory of lesser reserve" that suggests that patients can skip stages of emergence with lower brain reserve capacity and may lend up into more agitation on emergence.[20]

Limitations

There are many limitations to this study. It is a small cohort pilot study and hence the comparisons of various variables in both groups cannot be extrapolated. The findings of this small series should be interpreted with caution and considered as hypothesis generating for a larger multicentered study. In addition, this study period was limited to PACU and long-term follow-up was not available. As previously mentioned, the selection criteria for epilepsy surgery does preclude patients with significant neuropsychological deficits, and hence comparison between the patients with lower and higher neuropsychological profiles was not possible.

Conclusion

Emergence agitation is not uncommon in patients undergoing temporal lobectomy and AH. Patients who had severe agitation had the lowest IQ. However, due to the small sample size, the role of preoperative neuropsychologic profiles and hippocampal volumes in predicting the pattern of emergence is inconclusive. Future prospective studies would be useful to reveal predictors that could be linked with the emergence agitation in this patient population.

Ethical Approval

This study was approved by the institutional ethical committee under the ID: UHN REB # 14-8212BE, December 2, 2014.

Trial Registration

The study is registered at http://clinicaltrials.gov under registration ID NCT02360098.

Author's Contributions

LV and SBh contributed to the concepts, design, definition of intellectual content, literature search, clinical studies, data acquisition, data analysis, statistical analysis, manuscript preparation, manuscript editing, and manuscript review. SBa contributed to the definition of intellectual content, literature search, data analysis, statistical analysis, manuscript preparation, manuscript editing, and manuscript review. TC contributed to the design, definition of intellectual content, manuscript preparation, manuscript editing, and manuscript review. MPMcA contributed to the concepts, design, definition of intellectual content, clinical studies, data acquisition, data analysis, statistical analysis, manuscript editing, and manuscript review. TV contributed to the concepts, design, definition of intellectual content, clinical studies, data acquisition, manuscript editing, and manuscript review. LV serves as the guarantor of the research.

Conflict of Interest

None declared.

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