

Stereotactic Electroencephalography Is Associated With Reduced Pain and Opioid Use When Compared with Subdural Grids: A Case Series

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BACKGROUND: Minimally invasive surgery (MIS) has been shown to decrease length of hospital stay and opioid use.

OBJECTIVE: To identify whether surgery for epilepsy mapping via MIS stereotactically placed electroencephalography (SEEG) electrodes decreased overall opioid use when compared with craniotomy for EEG grid placement (ECoG).

METHODS: Patients who underwent surgery for epilepsy mapping, either SEEG or ECoG, were identified through retrospective chart review from 2015 through 2018. The hospital stay was separated into specific time periods to distinguish opioid use immediately postoperatively, throughout the rest of the stay and at discharge. The total amount of opioids consumed during each period was calculated by transforming all types of opioids into their morphine equivalents (ME). Pain scores were also collected using a modification of the Clinically Aligned Pain Assessment (CAPA) scale. The 2 surgical groups were compared using appropriate statistical tests.

RESULTS: The study identified 43 patients who met the inclusion criteria: 36 underwent SEEG placement and 17 underwent craniotomy grid placement. There was a statistically significant difference in median opioid consumption per hospital stay between the ECoG and the SEEG placement groups, 307.8 vs 71.5 ME, respectively ($P = .0011$). There was also a significant difference in CAPA scales between the 2 groups ($P = .0117$).

CONCLUSION: Opioid use is significantly lower in patients who undergo MIS epilepsy mapping via SEEG compared with those who undergo the more invasive ECoG procedure. As part of efforts to decrease the overall opioid burden, these results should be considered by patients and surgeons when deciding on surgical methods.

KEY WORDS: Epilepsy, Electrocorticography, Stereotactic electroencephalography, Opioid, Pain, Grid

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Approximately 3 million adults have epilepsy in the United States, and an estimated 30% have drug-resistant epilepsy (DRE), meaning they continue to have seizures despite treatment with ≥ 2 antiepileptic medications.¹⁻³ Among patients with DRE, surgery may be curative in up to 70%.²

An estimated 2000 to 3000 patients undergo surgical procedures for epilepsy each year.² To effectively treat epilepsy with surgery, the epileptogenic zone (EZ) must be identified and fully mapped. Laterality of the EZ can often be found by using noninvasive electroencephalogram (EEG), but because of the poor spatial resolution of scalp electrodes, intracranial placement of EEG electrodes may be required for precise anatomical EZ mapping.^{1,2}

The 2 predominant surgical methods for placing intracranial electrodes are electrocorticography (ECoG) and stereotactic electroencephalography (SEEG).⁴ ECoG is accomplished by craniotomy and placement of subdural electrodes. Grid-based ECoG allows a

ABBREVIATIONS: CAPA, Clinically Aligned Pain Assessment; CPT, Current Procedural Terminology; DRE, drug-resistant epilepsy; ECoG, electrocorticography; EEG, electroencephalogram; EZ, epileptogenic zone; ME, morphine equivalent; MIS, minimally invasive surgery; MME, milligrams of morphine equivalent; NRS, Numeric Pain Rating Scale; SEEG, stereotactic electroencephalography

wider and more specific description of surface electrical activity but can miss deeper EZs and requires more invasive surgery with more tissue trauma. SEEG involves stereotactically inserting electrodes through the skull into the brain via a minimally invasive approach.^{1,2,5} SEEG can detect EEG patterns arising from specific deep-seated targets through smaller incisions with less tissue disruption but does not easily capture a wide extent of superficial cortical activity, although it has been done well at high-volume centers. Although SEEG was previously widely adopted in Europe and Canada, over the past decade, it has become more widely used in the United States, when possible and appropriate for a patient's disease, because it is less invasive and possibly less painful.^{2,4-8}

The United States is currently facing dramatic increases in opioid addiction and opioid-related mortalities.^{9,10} Between 1999 and 2017, deaths attributed to opioid overdose quadrupled from 16 849 to 70 237 deaths/year.^{9,11,12} The birth of the opioid epidemic can be traced to the 2001 guidelines from the Joint Commission, which bound pain management to Medicaid/Medicare reimbursements,¹²⁻¹⁴ in conjunction with aggressive promotion by pharmaceutical companies, which resulted in an increase in opioid prescriptions for pain management.^{12,15} The increase was especially noticeable for patients undergoing surgery, as ~99% of adults undergoing surgery in the United States are prescribed opioids despite their marginal efficacy.^{12,16-18} The perioperative risk of addiction in opioid-naïve patients has been estimated to be 6% to 10%, and the risk of addiction increases significantly for those who use opioids after postoperative day 3 and most dramatically between days 5 and 31.^{9,12,19,20} Multiple methods have been proposed to decrease opioid use in surgical patients, including the use of nonaddictive pain medications such as nonsteroidal anti-inflammatory drugs (NSAIDs), ketamine, and gabapentin; meditation and mindfulness techniques; and preoperative counseling.²¹⁻²⁷

Given the addictive nature of opioids and prior studies and anecdotal experience suggesting that SEEG may be less painful than grids,²⁸ we sought to identify the prescription patterns at our institution and evaluate the effectiveness of different pain management strategies among adult patients who underwent intracranial electrode placement via ECoG and SEEG.²⁸ We hypothesized that opioid medications use would be lower in the SEEG cohort. We also compared the postoperative pain scores between the 2 groups to determine whether they were correlated with the amount of opioids prescribed during hospitalization. Lastly, we sought to identify the total amount of opioids given at discharge and determine whether this differed between groups.

METHODS

Approval for this nonconsecutive case series was obtained by the Institutional Review Board with a waiver of patient consent. A retrospective chart review was used to identify patients treated with SEEG (Current Procedural Terminology [CPT] code 61760) or ECoG (CPT

61533) from 2014 through 2018. The study design and proposal are registered at researchregistry.com (filing number 5971). Data collection was done between May 2019 and August 2019. The inclusion criteria were SEEG or ECoG surgery, age ≥ 18 yr, and diagnosis of epilepsy. The exclusion criteria were history of chronic opioid use defined as daily preoperative opioid use, complications occurring during surgery requiring additional surgery or cessation of seizure recording, and surgery that was not SEEG or ECoG. Patients were categorized by surgery type. All surgeries were performed by 2 physicians at our quaternary hospital that specialize in functional neurosurgery and had advanced command of the procedures. All patients were placed under general anesthesia; local anesthetics were used at the headframe pin sites after induction of general anesthesia to decrease postoperative pain from the headframe placement. For SEEG, planning was conducted using preoperative T1-weighted magnetic resonance imaging with contrast, the patient was fitted with a CRW frame (Integra LifeSciences, Princeton, New Jersey), and a high-resolution computed tomography scan was obtained for registration. SEEG electrodes were removed in the operating room under monitored anesthesia. For grid placement, the patient was fixed in a Mayfield head clamp (Integra LifeSciences, Princeton, New Jersey), registered for intraoperative neuronavigation, and a craniotomy was created in the desired location for the electrodes. Electrodes were removed under general anesthesia after a reopening of the craniotomy.

A power calculation was performed before the start of the study. Our calculation showed that a 30% difference in opioid use, measured as milligrams of morphine equivalents (MME), would provide a statistically meaningful difference. The sample size needed to detect a 30% difference, for an alpha of 0.05 and a power of 0.8, was 11 patients per arm.

Conventionally, patients who undergo SEEG or grid-based ECoG surgery will have a second surgery to remove the electrodes. To more accurately characterize pain management patterns, we separated the hospitalization into 4 time periods: the first postoperative period, defined as the first 8 h after surgery; the first interval period, which lasted from the end of the first postoperative period until the second surgery; the second postoperative period, defined as the first 8 h after the second surgery; and the second interval period, lasting from the end of the second postoperative period until discharge (Figure 1). The types and doses of pain medications administered during these time periods for all patients were collected, and total MMEs were calculated for all opioid-based medications. Pain data from the comfort category of the Clinically Aligned Pain Assessment (CAPA) survey were also collected for each of the 4 periods.^{29,30} The CAPA is a verified pain assessment tool used preferentially by our institution to assess a patient's pain.^{29,30} The comfort category of the CAPA was the only category included because it is the most closely related to the more traditionally used Numeric Pain Rating Scale (NRS).^{29,30} The comfort category of the CAPA was transcribed into a numbered ordinal scale, with 0 indicating negligible pain, 1 being comfortably manageable pain, 2 being tolerable pain with discomfort, and 3 indicating intolerable pain (Table 1).^{29,30}

The Wilcoxon rank-sum test for nonparametric data was used to compare the MMEs used between the 2 groups for the entire stay and for each interval. Spearman's correlation was used to determine correlation between the average comfort category CAPA score and the total MMEs for each interval. The demographic information of the 2 groups was evaluated to identify any confounding variables. Length of stay was significantly different between groups; thus, the total MMEs for the entire stay were divided by the length of stay for each patient to create a new variable measuring MMEs administered per day. The difference

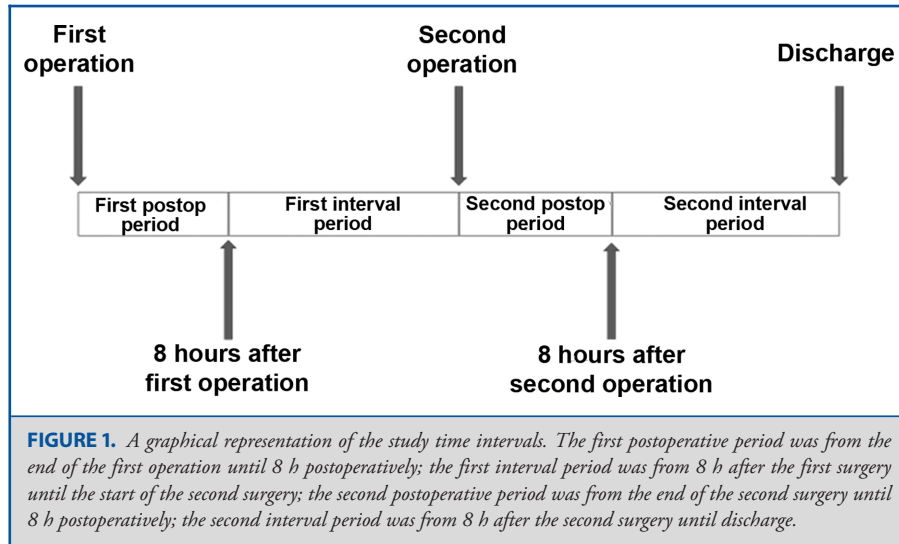


TABLE 1. The Comfort Category of the CAPA Tool

Response	Numeric equivalent	NRS equivalent
Intolerable	3	9-10
Tolerable with discomfort	2	6-8
Comfortably manageable	1	3-5
Negligible pain	0	1-2

The CAPA grade was transformed into a number corresponding with the pain level for the purposes of statistical interpretation. Correlation to the NRS is also shown.

between the MMEs used per day in each surgical group was tested for significance using the Wilcoxon rank-sum test. A nonparametric equality of means test was performed to evaluate whether there was a difference in the total median MME use between periods in each surgical group. Stata IC version 15.1 (StataCorp, College Station, Texas) was used for all statistical calculations. The strengthening the reporting of observational studies in epidemiology checklist was used to ensure the study design complied with current best-practice guidelines for retrospective cohort studies.

RESULTS

Patient Cohort

This was a retrospective cohort case series study at a single academic center designed to identify whether there is a difference in opioid use between adult patients undergoing SEEG and those undergoing grid-based ECoG placement for seizure focus localization. It was powered to identify a 30% reduction in opioid use between the 2 groups. We identified a total of 53 patients who met the following inclusion criteria: 36 patients in the SEEG group and 17 patients in the ECoG group. The overall demographics of the 2 groups are shown in Table 2. The major differences between

the 2 groups include the number of electrode contacts implanted with the SEEG group, which had a higher number on average, 93, when compared with the ECoG group on average, 66 ($P < .002$). There was also a difference in the surgical laterality, with the SEEG group having a higher proportion of bilateral surgeries than the ECoG group (80.6% vs 23.5%; $P < .001$). The duration of surgery was also different between the groups; the median surgical duration for the ECoG group was longer than that of the SEEG group (339 vs 260 min; $P = .0245$). Otherwise, the groups were fairly well matched, with no difference in the mean age, sex, type of seizures, median number of seizures recorded, median preoperative modified Rankin Scale score, mean number of antiepileptic drugs used preoperatively, and complications.

There were 3 total complications encountered in this cohort: 2 in the SEEG group and 1 in the ECoG group. The SEEG complications were 1 subarachnoid hemorrhage that was found on postoperative computed tomography head but did not result in any neurological deficits, and 1 subdural hygroma that formed after electrode placement and caused some mild right upper-extremity weakness that resolved; seizure recording was continued as planned in both cases. The one complication in the ECoG group was mild right-sided weakness postoperatively that improved; seizure recording was performed as planned. A flow diagram showing the inclusion and exclusion of patients can be found in Figure 2.

Three patients were excluded from the overall study cohort: one because of an epidural hematoma that occurred after a seizure that resulted in early termination of ECoG seizure recording and a unplanned evacuation of the epidural hematoma; a second because of an intraoperative hemorrhage during SEEG implantation that required the procedure to be aborted, although no further surgery was necessary; and a third because of chronic use of opioids for the treatment of migraines prior to initial hospitalization.

TABLE 2. Demographic Data for the SEEG and ECoG Groups

	SEEG (n = 36)	ECoG (n = 17)	P value ^a
Mean age (yr)	32.1 ± 8.2	32.9 ± 9.8	.7514
Sex (% male)	52.8% (n = 19)	35.3% (n = 6)	.257
Type of seizure (% focal)	47.2% (n = 17)	58.8% (n = 10)	.130
Surgical laterality	Bilateral: 80.6% (n = 29) Left: 11.1% (n = 4) Right: 8.3% (n = 3)	Bilateral: 23.5% (n = 4) Left: 23.5% (n = 4) Right: 52.9% (n = 9)	<.001
Median number of seizures recorded	5.5 ± 6.8	6 ± 6.8	.977
Median preoperative modified Rankin Scale score	1 ± 0.65	2 ± 0.86	.0971
Mean number of antiepileptic drugs used preoperatively	2.8 ± 1.3	2.8 ± 1.5	.893
Mean length of surgery (min)	260 ± 108	339 ± 130	.0245
Mean number of electrode contacts implanted	93 ± 21	66 ± 36	<.002
Number (%) of complications	1 (2.8%)	2 (11.7%)	.238

^aP values are included to show differences between groups and not for inferential purposes.

Data are reported as mean ± SD unless otherwise indicated.

Significant values are shown in boldface type.

MME Consumption

A general overview of the comparison between the 2 groups is presented in Tables 2 and 3. The median MME consumed in the SEEG cohort was significantly lower than that consumed in the ECoG cohort (71.5 vs 307.8 MME, respectively; $P = .0011$, Wilcoxon rank-sum test). This difference was observed across every epoch (Figure 3). To control for length of stay, MMEs per day were calculated. This measure was also significantly lower for SEEG than grids when comparing the median MME per day (16.4 vs 54.4 MME/day, respectively; $P = .0377$, Wilcoxon rank-sum test).

Non-Narcotic Pain Medication Use

The median total NSAID use among all patients in both groups was 0 mg for the entire hospitalization. When comparing the mean NSAID use in each group, the SEEG group had a lower mean of 1.7 mg throughout the hospital stay, whereas the ECoG group had a mean use of 275 mg. The median total acetaminophen use among the SEEG group was lower (4.9 g for the entire stay) when compared with ECoG (11.7 g; Table 3).

CAPA Pain Scale Score

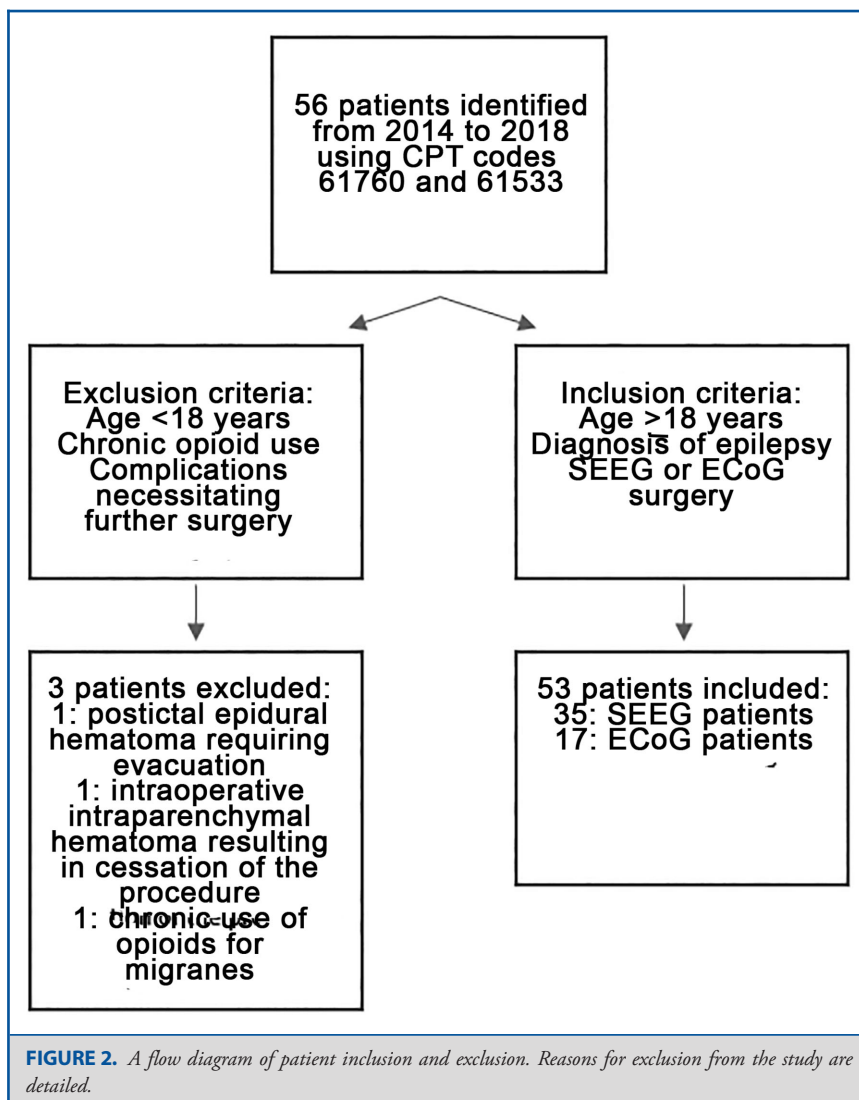
The average comfort category of the CAPA pain scale scores for the entire stay correlated with the total MMEs used during the entire stay for both the SEEG and the ECoG groups (Spearman correlation coefficient $\rho = .52$, $P = .0012$; $\rho = .56$, $P = .02$, respectively; Table 4). The only other significant correlation was found between the comfort category CAPA scores and total MME used for the first epoch in the SEEG cohort, ie, the time period between 8 h after the first surgery and the start of the second surgery ($\rho = .51$, $P = .002$). Total MMEs prescribed at discharge were also calculated by cohort, and the median total MMEs at discharge were significantly different (SEEG 112.5 vs ECoG 450 MMEs; $P = .02$). There was a statistically significant difference

in the comfort category CAPA score between the means of the SEEG group and ECoG group (0.8 vs 1.2; $P = .0117$).

DISCUSSION

Surgical treatment can result in seizure freedom for patients with DRE, which leads many epilepsy patients to pursue surgical options.^{2,3,6} Before offering surgical resection or neuromodulation, a precise delineation of the seizure onset zone is crucial. When noninvasive workups fail or produce discordant results, intracranial monitoring is often the next step. This can be done with either penetrating depth electrodes (SEEG) or subdural epicortical electrodes (ECoG). At our institution, SEEG is typically used in cases where there is a strong network hypothesis, a hypothesized deep seizure focus, concern for bilateral foci, or the need to map within a prior craniotomy. Grids are used when there is a stronger lateral cortical hypothesis, a need to estimate the extent of a putative neocortical resection zone, or a desire to map eloquent function near a putative resection zone. ECoG appears to have a higher rate of CSF leak when compared with SEEG, 12% vs 0.3%, a higher hemorrhage rate (4% vs 1.4%), a higher infection rate (2% vs <1%), and is anecdotally more painful.^{28,31,32}

The current study was designed to identify whether SEEG procedures led to a reduced use of opioids compared with craniotomy-based ECoG procedures during hospitalization. The primary endpoint of this study, the difference in the median total MMEs, was significantly lower in the SEEG group when compared with the ECoG group, in both the unadjusted and the adjusted length of stay calculations (Table 3). This finding implies that SEEG can significantly reduce opioid use during hospitalization for epilepsy surgery. The observed 74% median reduction in total MMEs per stay was larger than we hypothesized when designing the study. The amount of medication



prescribed at discharge also differed significantly between the 2 groups, with the SEEG group receiving fewer total opioids at discharge than the ECoG group (Table 3). Another recently published study performed by Wang et al²⁸ also demonstrated a significant difference in the opioid use between those patients undergoing SEEG and those undergoing ECoG procedures, and those findings validate our results.

We attempted to correlate the pain scores recorded during the patients' stays with the total MMEs given during the stay and found correlations between the average overall pain score and total MMEs given for both the SEEG and ECoG cohorts, as well as during the first time period in the SEEG cohort. None of the other periods demonstrated a significant correlation between the pain scores recorded and the total MMEs, which may be due to the small sample size of the individual groups. Indeed, although this study was not powered to identify a correlation

between the individual time periods, we did find a statistically significant difference in the total median MME use between the periods in each group, with more MME being used in the first interval period. This first interval typically takes place during the main portion of the patient's stay. Additionally, there was a significant difference in the comfort category CAPA score between the 2 surgical groups, with the SEEG group reporting lower pain scores overall. This finding suggests that the reason the SEEG group received a significantly lower median of opioid medication throughout their stay is that the procedure itself resulted in less pain experienced overall. This supports our expectation that the minimally invasive procedure is less painful and may be a successful opioid reduction strategy. Wang et al²⁸ also found a significant difference in pain scores between the 2 groups and demonstrated that the ECoG group had a higher overall pain score throughout their stay, though this was measured using the

TABLE 3. Statistical Comparisons between the SEEG and ECoG Groups			
Variable	SEEG (n = 36)	ECoG (n = 17)	P value^a
MME			
Total	71.5 ± 543.1	307.8 ± 296.3	.0011
First PO period	7.9 ± 34.6	17 ± 15.5	.0107
First interval period	52.72 ± 488.5	182.5 ± 236.3	.0089
Second PO period	0 ± 18.2	10.35 ± 15.0	.0012
Second interval period	0 ± 56.6	67.5 ± 84.6	<.001
Discharge total	112.5 ± 249.7	450 ± 543.2	.020
MME per day	16.4 ± 38.2	34.9 ± 69.4	.0377
Total NSAIDs (mg)	0 ± 7.0	0 ± 1065.1	.3823
Total acetaminophen (g)	4.9 ± 11.8	11.7 ± 7.8	.0055
Length of stay (d)	6 ± 3.7	8 ± 8.9	.0335
Mean comfort category CAPA score	0.8 ± 0.4	1.3 ± 0.6	.0117

PO, postoperative.

^aP values are included to show differences between groups and should not be included for inference.

Significant values are shown in boldface type.

Data are reported as median ± SD unless otherwise indicated.

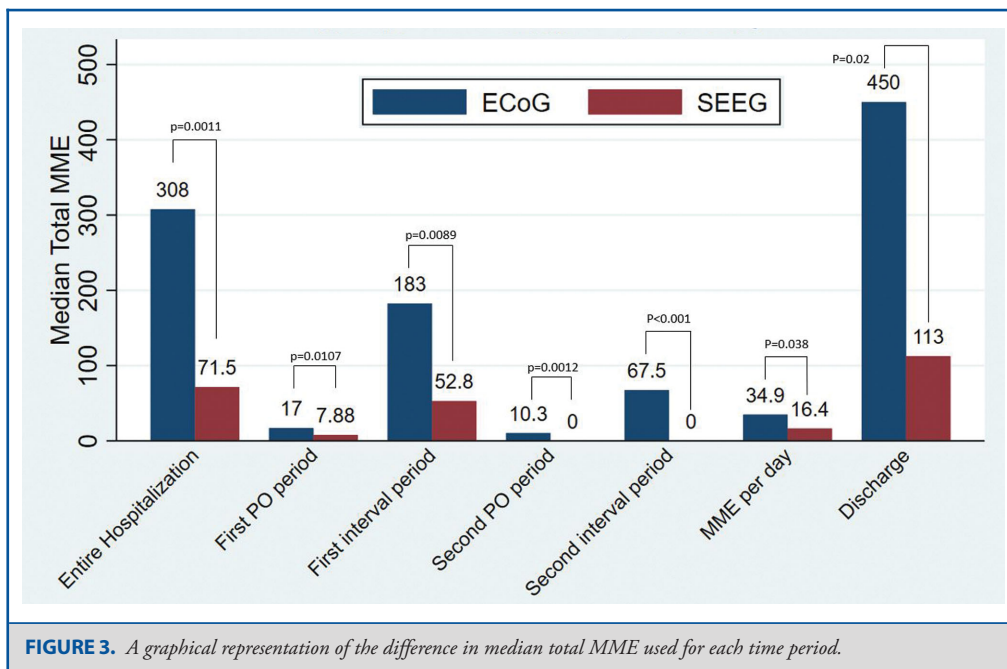


FIGURE 3. A graphical representation of the difference in median total MME used for each time period.

NRS rather than CAPA. They also did not find any correlation between the pain scores and amount of opioids used, which may suggest that surgical pain management strategies are mostly protocol driven and are not necessarily adaptive to the needs of the patient.

The use of non-narcotic pain medications is a first-line method in opioid reduction and significantly decreases the amount of opioids used in surgical patients. Specifically, NSAIDs are a mainstay in pain management. Despite many studies demonstrating the efficacy and safety of NSAIDs in the treatment

of postoperative pain management, their use in neurosurgical patients has not been widely adopted. This is likely secondary to partial platelet inhibition that occurs with NSAIDs. Our study underlines the lack of NSAID use in neurosurgical patients, with low usage in both SEEG and ECoG cohorts. In fact, the median amount of NSAIDs used was 0 mg, demonstrating this avoidance of NSAIDs. Wang et al²⁸ described their lack of NSAID use as well, stating that they did not use any NSAIDs in their postoperative patients. As neurosurgical providers, we should reconsider our stance on NSAIDs in postoperative pain management to

TABLE 4. Correlations Between Comfort Category CAPA Pain Score and Total MMEs Used in Each Corresponding Time Interval

Time period	SEEG		ECoG	
	CAPA average	Spearman's correlation to concurrent operative interval ^a	CAPA average	Spearman's correlation to concurrent operative interval ^a
Overall	0.8	Rho = 0.5184 P = .0012	1.2	Rho = 0.5567 P = .0203
First PO	1.3	Rho = 0.2685 P = .1247	1.6	Rho = 0.1102 P = .6958
First interval	1.1	Rho = 0.5115 P = .0020	1.2	Rho = 0.1643 P = .5585
Second PO	1.1	Rho = 0.3286 P = .2140	1.8	Rho = 0.1142 P = .7237
Second interval	1.4	Rho = -0.6150 P = .1046	1.4	Rho = 0.3189 P = .3391

PO, postoperative.

^aSpearman's test of correlation by surgical group.

Significant values are shown in boldface type.

further decrease the use of opioids in our patients. To increase their use and potentially decrease the use of opioids, a computed tomography scan could be obtained postoperatively to confirm the lack of intraoperative hemorrhage, and then NSAIDs could be prescribed with more confidence that hemorrhagic complications would not occur or be exacerbated.

Limitations

The main limitation of this study is that it is a single-center, retrospective review that introduces institutional and selection bias. Although we powered our study to identify a 30% decrease in MME use—which we found to be significant—we lacked sufficient power to identify other differences identified in this study, including correlation between pain scores and the amount of opioids used and a difference in pain scores between the 2 groups.

CONCLUSION

The results of this study imply that the use of opioid pain medications is lower in those patients undergoing SEEG procedures for seizure localization when compared with those undergoing ECoG. Although subdural grids and SEEG are not interchangeable, the considerable reduction in postoperative pain and opioid use with SEEG should play a role in surgical decision making.

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COMMENT

This retrospective study focused on periprocedural pain in a cohort of patients with epilepsy undergoing invasive monitoring for drug-refractory epilepsy. The authors succeed to objectify implanters' observations and anecdotal reports that stereoelectroencephalography patients fare better with respect to pain perception and need for opioids. Oftentimes regarded as 'expected conditions', previous studies comparing various invasive monitoring techniques insufficiently appreciated patients' discomforts during their epilepsy monitoring unit stay. The factor 'pain' should be kept in mind when the epilepsy surgery group discusses their implantation strategy. However, the ultimate decision whether to implant subdural grids or use stereoelectroencephalography should primarily be made on the grounds of which technique is most suitable to delineate the putative epileptogenic zone in each individual case.

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