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Editorial

Mitigating the risk of triggering intraoperative seizures with cortical stimulation

See Article, pages 1058–1065

Intraoperative cortical electrical stimulation enables functional mapping during brain surgery, but often triggers localized electrocorticographic (ECoG) afterdischarges that sometimes progress to focal or secondarily generalized clinical seizures. These discharges arise more frequently with traditional Penfield 50–60 Hz stimulation lasting seconds than with very brief high-frequency multipulse stimuli for motor evoked potentials (MEPs). They may resolve spontaneously or after cold irrigation and anticonvulsants, and have no reported sequelae. However, clinical seizures could cause harmful complications, and discharge spread to unstimulated cortex can cause false Penfield technique localization. Furthermore, post-ictal depression or treatment side effects could cause mapping failure by reducing cortical excitability or patient testability. Consequently, it is critical to identify risk factors for, and means of protection against afterdischarges and seizures.

In this issue of *Clinical Neurophysiology*, Dineen et al. (2019) provide important new evidence on this topic from a large retrospective study of 544 monitored brain surgeries done for diverse cerebral lesions in various lobes. They included awake and anesthetized patients with and without a history of epilepsy and with or without preoperative anticonvulsant maintenance or loading. In addition, they evaluated both bipolar Penfield technique using 60 Hz biphasic 1 ms pulses and anodal multi-pulse MEP technique using 6 monophasic 0.5 ms pulses at 250 Hz with a 2 Hz repetition rate. Notably, they applied multivariate logistic regression to identify independently significant risk factors for seizure induction, defined as a >10 s afterdischarge.

The most important new finding was a protective effect of prophylactic anticonvulsant loading before surgery (odds ratio 0.55, $p < 0.01$). Thus, this intuitively logical approach may approximately halve the risk of seizures, and could be a good general recommendation. The authors advise intravenous levetiracetam due to its favorable pharmacokinetics, absent drug interactions and limited side effects.

Another novel result was greater seizure induction risk with lesions having diffuse infiltrative margins on MRI (odds ratio 2.42, $p < 0.01$). This suggests that particular care might be advisable for these patients.

Although not a new finding, the results also confirm greater seizure risk with Penfield than multi-pulse stimulation (odds ratio 1.97, $p = 0.01$), reinforcing this uniform conclusion in previous reports (MacDonald, 2002; Neuloh et al., 2004; Szelényi et al., 2007; MacDonald and Deletis, 2008; MacDonald et al., 2013). In view of the large sample size, this adds substantial weight to an emerging consensus that safer multi-pulse MEP and other evoked potential methods are preferable for mapping primary functional cortex, while more dangerous Penfield technique should be limited to mapping language and other associative cortical functions for which there is so far no satisfactory alternative.

There were also relevant negative results. In particular, there was no correlation of induced seizures to preoperative epilepsy or anticonvulsant maintenance, which disagrees with some previous reports (e.g., Lesser et al., 2008), but agrees with others (e.g., Szelényi et al., 2007). Thus, these factors appear to have questionable significance and it would be unjustifiable to deny patients mapping because of them. Also, while the awake state correlated with more induced seizures when analyzed as a single variable, this correlation fell away on multivariate analysis because these patients often had Penfield stimulation. In addition, specific pathology did not influence seizure risk, which is surprising as some lesions are more epileptogenic than others.

One perplexing result was a 25% incidence of seizure induction, which is substantially greater than previously reported rates of 5–20% with Penfield and 0–5% with multi-pulse technique (Sartorius and Wright, 1997; Sala and Lanteri, 2003; Neuloh et al., 2004; Szelényi et al., 2007; MacDonald et al., 2013; Abalkhail et al., 2017). The authors suggest that this could be partly due to their high-risk tertiary care patient population, but other specialized centers studying this issue have similar patients. More likely it is mainly due to the >10 s afterdischarge seizure definition. Traditionally, 'afterdischarge' refers to clinically silent ECoG patterns of variable duration, while 'seizure' implies clinical signs. However, afterdischarges are seizure patterns because they evolve in frequency, amplitude and distribution, and commonly progress to clinical manifestations. Thus, the distinction is somewhat arbitrary, and the reasonably chosen seizure definition can account for most of the discrepancy with other reports using traditional definitions. Notably, in Fig. 1 of the article, cold irrigation was called for in <10 s, suggesting that most afterdischarges were treated as seizures. This reliance on ECoG for seizure diagnosis is not universal. For example, some consider it to be optional for multi-pulse MEPs because afterdischarges do not cause false localization with this

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technique and induced motor seizures are quickly evident in muscle recordings (MacDonald et al., 2013). Nevertheless, ECoG is essential for Penfield technique to avoid false localization (MacDonald and Deletis, 2008) and its use for multi-pulse technique might enhance safety by enabling earlier seizure detection.

Another possible contributing factor for the high seizure incidence might have been the use of 6 pulses and a 2 Hz repetition rate for multi-pulse stimulation. Reports with fewer seizures generally apply $\leq$5 pulses and in my experience, $\leq$1.5 Hz rates seem less prone to incite seizures, but determining if these parameter differences are actually relevant requires further study. Some other parameter questions also remain unexplored. For example, perhaps 0.2 ms pulses that are near to mean MEP chronaxie might reduce seizure incidence by minimizing threshold charge and energy (Abalkhail et al., 2017). Also, since the authors point out that current density may be relevant, perhaps larger 1 cm^2 electrodes to reduce current density could be safer. Or, maybe awake patients who presumably do not need multi-pulse stimuli for eliciting MEPs could undergo very safe motor cortex mapping with single pulses that rarely induce seizures (MacDonald, 2002).

Although not providing all the answers and despite its retrospective design, this impressive study advances our understanding of intraoperative cortical stimulation, and along with future research of its kind may help us to mitigate, but probably not eliminate, the risk of triggering intraoperative seizures.

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Conflict of interest

None.

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