

RANDOMIZED CONTROLLED TRIAL OF PROPHYLACTIC PHENYTOIN AFTER NEUROSURGERY FOR BRAIN TUMOR

Add-on Phenytoin Fails to Prevent Early Seizures after Surgery for Supratentorial Brain Tumors: A Randomized Controlled Study

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PURPOSE: To determine the potential effectiveness of phenytoin (PHT) in preventing early postoperative seizures in patients undergoing craniotomy for supratentorial brain tumors. Two hundred patients requiring elective craniotomy for supratentorial brain tumors were randomized to two groups of equal size, with a prospective, open-label, controlled design. One group received PHT (18 mg/kg as an intravenous intraoperative load, followed by additional daily doses aimed at maintaining serum PHT concentrations within the 10- to 20- μ g/ml range) for 7 consecutive days. In the other group, PHT was not administered. More than 90% of patients in both groups continued to take preexisting anticonvulsant medication (AEDs) with carbamazepine or phenobarbital throughout the study. The primary efficacy end point was the number of patients remaining free from seizures during the 7-day period after the operation. Of 100 patients allocated to PHT, 13 experienced seizures during the 7-day observation period, compared with 11 of 100 patients in the placebo group ($p > 0.05$). Most seizures occurred in the first day after surgery in both groups. There were no differences between groups in the proportion of patients experiencing more than one seizure, but there was a trend for generalized seizures to be more common in PHT-treated patients than in controls (11 vs. five patients, respectively). Status epilepticus occurred in one patient in the PHT group and in two patients in the control group. Of the 13 PHT-treated seizure patients, 11 had serum PHT concentrations within the target range, and only two had concentrations below range on the days their seizures occurred. PHT, given at dosages producing serum concentrations within the target range, failed to prevent early

postoperative seizures in patients treated with concomitant AEDs. Prophylactic administration of PHT cannot be recommended in these patients.

COMMENTARY

There continues to be clinical controversy about whether anticonvulsants should be used prophylactically to prevent seizure occurrence in the post-operative period: Do they prevent seizures immediately post-surgically or do they provide any anti-epileptogenic effect in the long term? Temkin et al. (1) and Iudice and Murri (2) reported usefulness of phenytoin for prevention of seizures in head trauma. This article reports a prospective randomized study of neurosurgical patients in the immediate seven days after removal of supratentorial brain tumors noting that the highest incidence of postoperative seizures is within the first 48 hours postoperatively and that seizures may increase the morbidity of the postoperative course.

One hundred patients randomized to receive intravenous phenytoin (PHT) received loading doses preoperatively and were maintained at therapeutic levels with IV or oral dosing with levels measured on postoperative day 1, 2, and 6. One hundred patients in the control did not receive PHT and were observed. The groups did not differ significantly demographically, clinically, or with respect to tumor types or locations. Most patients were on preoperative carbamazepine (CBZ) and/or phenobarbital (PB) which were not adjusted during the study and patients were excluded who had had seizures for the seven days prior to surgery. The study was terminated early due to the lack of statistical difference on interim analysis between the groups: 13% incidence of seizure in the PHT-treated group and 11% incidence of seizures in the control group. Seizures were most often generalized, either partial with secondary generalization or generalized at onset. Although the actual numbers were small, preventing statistical comparisons, the risk of early seizure was greatest in the first 24 hours postoperatively; in extratemporal tumors, especially frontal locations; in tumors in which the tumor was incompletely removed; in tumors which had shown contrast enhancement on imaging, and in tumors in

which removal had involved dissection through the cortex. In the treated patients, PHT concentration were kept between 10–20 $\mu\text{g/ml}$ but there was no information given to evaluate if there was a difference in response between those who had “high” concentrations and those who had usual 10–20 $\mu\text{g/ml}$ ranges. No information was given regarding used of benzodiazepines, hyperventilation, or steroid use. Complication rates did not differ. These patients did not have their seizures monitored so we do not have information as to whether they were similar to the preoperative seizure type or were a new event for the patient. Long-term outcome for these patients was not reported.

This is the first controlled large neurosurgical series with monitored concentrations of PHT to evaluate postoperative seizure prophylaxis in tumor surgery. It does not answer the question of long-term anti-epileptogenesis and does not answer

the question for any anticonvulsants other than PHT. Would higher therapeutic level of PHT, e. g., 18–24 $\mu\text{g/ml}$, or use of potentially neuroprotective new generation anticonvulsant drugs have produced different results? Future studies addressing these questions will be most useful.

References

1. Temkin NR, Dikmen SS, Wilensky AJ, et al. A randomized, double-blind study of phenytoin for the prevention of post-traumatic seizures. *N Engl J Med* 1990;323:497–502.
2. Iudice A, Murri L. Pharmacological prophylaxis of post-traumatic epilepsy. *Drugs* 2000;59:1091–1099.

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