Editorial

Post-operative seizure prophylaxis in gliomas

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Comment on: Dewan MC, White-Dzuro GA, Brinson PR, *et al*. The Influence of Perioperative Seizure Prophylaxis on Seizure Rate and Hospital Quality Metrics Following Glioma Resection. Neurosurgery 2017;80:563-70.

Submitted Jun 14, 2017. Accepted for publication Jun 19, 2017.
doi: 10.21037/tcr.2017.06.51
View this article at: http://dx.doi.org/10.21037/tcr.2017.06.51

The role of prophylactic anti-epileptic drugs (AEDs) in patients with brain tumours in the post-operative period is a vexed issue. Post-operative prophylaxis can be dichotomised into short term peri-operative prophylaxis lasting 1–2 weeks and longer-term prophylaxis lasting several months. The choice of drug, dose and length of treatment differs institution to institution and surgeon to surgeon. Over the last decade levetiracetam has really become the standard first line treatment offering some treatment consistently, however this is driven largely by expert opinion rather than high-level evidence data (1).

Rates of post-operative seizures in patients with gliomas without pre-operative seizures vary in the literature from 4–40% in the year following resection (2-8), with the first post-operative seizure generally occurring within the first month after craniotomy (9). A 2015 Cochrane review examined AED prophylaxis post craniotomy, regardless of the surgical indication (9). Unfortunately, the current evidence was limited by: different methodologies, heterogenous pathologies and inconsistent reporting of outcomes. Overall, it was concluded that there was limited evidence to support AED prophylaxis post craniotomy.

In the case of brain tumours specifically, practice guidelines based on randomised controlled trials (RCTs) and meta-analyses also don't support AED prophylaxis (10,11). However, these trials used older AEDs, included non-glioma pathologies and often examined the period after diagnosis, rather than strictly post-craniotomy. In addition, a large number of these studies lack a statistical plan with power analysis to determine adequate sample size; and power is often poor given the infrequent nature of post-operative of seizures in this cohort (12).

Given the controversy in this area, prophylactic AED use is still quite widespread. An online survey of 144 American Association of Neurological Surgeons revealed that while 63% of respondents 'almost always' prescribe post-operative AEDs for a supratentorial tumour, only 38% believed treatment significantly reduced the risk of post-operative seizures (13).

The role of short term peri-operative prophylaxis has been best examined by two RCTs (7,14), one large retrospective study (15) and by the more recent analysis by Dewan and colleagues (16). These studies deserve particular attention.

Wu *et al.*, enrolled 43 patients with a supratentorial glioma without pre-operative seizure (7) and randomised patients to 7 days of phenytoin or observation. In first post-operative week, 9% on phenytoin and 13% of observed patients experienced a seizure, a difference which was not statistically significant.

Iuchi and colleagues performed a RCT comparing 7 days of levetiracetam with 7 days of phenytoin for prevention of post-operative seizures in patients with brain tumours (14). This was a heterogenous population, with only 51% having a glioma. Twenty-seven percent had experienced a pre-operative seizure and were already on AED, which

questions whether this is a true prophylaxis trial. Overall, 1 (1.4%) patient taking levetiracetam and 11 (15.1%) taking phenytoin experienced a peri-operative seizure within 7 days (P=0.005). Although subgroup analysis in gliomas wasn't performed, in the whole cohort pre-operative seizure and pathology did not predict the peri-operative seizures rate.

Finally, Skardelly and colleagues performed a large single centre, retrospective observational study and examined early post-operative seizures within the first week (15). Two hundred and twenty-six patients with grade I–IV gliomas (184 grade III–IV) and without pre-operative seizure were examined. Seven percent of grade III–IV patients and 11% of grade I–II patients experienced an early seizure. A risk model analysis including a further 112 patients with metastases was performed and identified smaller tumours, gliomas and complete resection as predictors of early post-operative seizures, while AED use was not a predictive factor.

These studies set the scene for the recent paper from Dewan *et al*. (16). In a large retrospective observational study, the authors have again attempted to clarify the issue of peri-operative AED treatment. Dewan *et al*. examined the rate of seizure within 14 days of operation in patients with a grade I–IV supratentorial glioma undergoing craniotomy and resection. Unlike previous studies they included important hospital quality metrics as secondary outcomes: length of hospital and intensive care unit (ICU) stay, discharge disposition, 90-day emergency department (ED) visitation and unplanned readmission.

Three hundred and forty-two patients were analysed, giving this study one of the largest glioma cohorts in the peri-operative treatment literature. The cohort consisted primarily of grade IV gliomas (57%), but also included grade I (6%) and ependymomas (6%), which unfortunately adds some heterogeneity to the study population. Importantly, the cohort included patients with (n=149) and without (n=189) pre-operative seizure.

The decision to provide peri-operative AED was made by the treating neurosurgeon. This was characterised by seven days of levetiracetam administered as either new monotherapy (prophylaxis), add-on (for patients already on AED but not levetiracetam) or uptitration (for patients already on levetiracetam). Overall, 97% of patients with pre-operative seizure and 82% without pre-operative seizure received levetiracetam.

Eighteen patients (5.4%) experienced seizures within 14 post-operative days and peri-operative levetiracetam had no impact on seizure frequency. The cohort without pre-operative seizure were examined separately, although the baseline characteristics of this subgroup with respect of levetiracetam treatment were not described. Yet, the overall 14-day seizure rate was 4.7% and again levetiracetam had no effect. Peri-operative levetiracetam also had no impact on the resource utilization and quality hospital metrics in the whole cohort and the subgroup without pre-operative seizure.

In this large retrospective analysis, Dewan *et al*. have shown that peri-operative levetiracetam does not influence both the early post-operative seizure rate or hospital quality metrics. This study shares similar limitations to others in the literature. There is a heterogeneity in glioma grades with a predominance of grade IV tumours. As with previous peri-operative treatment studies, which have included 65–80% grade IV gliomas (7,14,15) generalisability of these findings beyond high-grade gliomas is in question.

The inclusion of patients with pre-operative seizure already on AED combines a population with treated tumour associated epilepsy, with those who have never experienced a seizure. The fact that both Dewan *et al*. and Iuchi *et al*. did not find pre-operative seizure to be associated with early post-operative seizure is telling (14,16). It suggests that early peri-operative seizures may not be influenced by the epileptogenicity of the lesion, but rather may represent acute symptomatic post-operative seizures. This is further supported by the lack of predictive power of Dewan's 'high risk epilepsy factors', Skardelly's seizure association with complete resection (15) and the fact that pre-operative seizure is one of the strongest predictors of long-term post-operative seizure outcome (3,8,17).

Taken together, early post-operative seizures are uncommon in gliomas undergoing resection and the evidence is conflicting on whether AED prophylaxis prevents peri-operative seizures. Dewan *et al*. add further evidence to support that add-on AED treatment doesn't influence the peri-operative outcome. The authors should be commended for the novel analysis of quality metrics; this can give confidence to clinicians that regardless of their treatment practice, healthcare utilisation may well be unaffected. However, it is important to remain mindful of the potential harm associated with prophylaxis, even for a well-tolerated drug such as levetiracetam. Neurocognitive side effects can occur in approximately 10% of epilepsy patients taking levetiracetam (18), with rates reaching close to 45% in brain tumour patients from RCT data (19). Dewan and colleagues quite rightly point out that without

high-quality evidence demonstrating a clear benefit, we should all be reconsidering the role of prophylactic AEDs.

An important question that remains is whether peri-operative treatment influences long-term seizure outcome, that is, is there an anti-epileptogenic effect of AED prophylaxis? Wu *et al*. noted that 7 days of peri-operative phenytoin compared with observation did not altered the rate of post-operative seizures after 30 days (7). However more work, with longer follow up periods, is clearly needed and it may be that medications targeting glioma driven glutamate alternations, such as perampanel, will offer the best chance of anti-epileptogenesis.

What is clear, is that further evidence from good quality prospective trials is required to ascertain the effectiveness of AED compared to placebo in preventing post-operative tumour associated epilepsy in patients without pre-operative seizure. A RCT is currently ongoing in patients with glioblastomas comparing lacosamide to placebo with completion estimated for mid 2018 (NCT01432171).

In addition, identifying high-risk groups for post-operative seizure will help individualise the use of AED prophylaxis (15). Elevated glutamate in the peritumoural region shows promise as a possible biomarker for post-operative seizures (20-22). Our research group is about to commence a phase II RCT comparing perampanel with placebo in grade II–III glioma patients without pre-operative and we will be utilising novel glutamate biomarkers (ACTRN12617000073303).

For the time being though, the question of AED prophylaxis in gliomas is still not definitively answered, but as Dewan and colleagues point out "*with such a well-tolerated drug in levetiracetam, if even a miniscule protective effect is believed, the use of AED prophylaxis will probably resume*".

Acknowledgments

Funding: Dr Andrew Neal was supported by an Australian Government Research Training Program Scholarship and by the Royal Melbourne Hospital Neuroscience Foundation.

Footnote

Provenance and Peer Review: This article was commissioned and reviewed by the Section Editor Xian-Xin Qiu (Shanghai Proton and Heavy Ion Center (SPHIC), a.k.a. the Proton and Heavy Ion Center of Fudan University Shanghai Cancer Center (FUSCC), Shanghai, China).

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2017.06.51). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Neal A, Kwan P, Morokoff A, O'Brien TJ. Post-operative seizure prophylaxis in gliomas. Transl Cancer Res 2017;6(Suppl 6):S1006-S1009. doi: 10.21037/tcr.2017.06.51

