Incidence and clinical decision making for the Wada test over one decade: 1997-2007

Rohit R. Das¹,², Andreas V. Alexopoulos³, Tobias Loddenkemper¹,²

¹ Department of Neurology, Division of Epilepsy and Clinical Neurophysiology, Children’s Hospital, Boston
² Department of Neurology, Harvard Medical School, Boston
³ Epilepsy Center, Cleveland Clinic Neurological Institute, Cleveland, USA

ABSTRACT – Purpose. The objective of this study was to review the percentage of Wada tests performed on patients with intractable temporal lobe epilepsy undergoing surgery at a single epilepsy centre over the last decade, and to identify clinical features which are more likely associated with decision making in favour of Wada testing. Methods. We retrospectively reviewed all temporal lobe resections performed between 1997 and 2007 at the Cleveland Clinic Epilepsy Center. Results. A total of 410 Wada tests were conducted on 777 patients undergoing temporal lobectomy (TL). Left temporal resection was performed in 55% of cases. The most frequent pathological diagnoses were hippocampal sclerosis (42%) and non-specific gliosis (26%). Overall, Wada test frequency in patients undergoing presurgical evaluation decreased over time. In 1997, 47 of 58 (81%) TL patients underwent Wada testing compared to 11 of 76 (14.4%) in 2007. Patients with left temporal lobe epilepsy, and/or those referred for subdural electrode placement, were significantly more likely to undergo Wada testing. The most common types of surgery were anteromedial temporal resection with removal of mesial structures (59%) and temporal resection without mesial structure removal (32%). Patients with left temporal epilepsy and Wada testing were significantly more likely to undergo resection of mesial cortex. Discussion. Wada testing has declined over the last decade in this single centre study. Patients with left, likely dominant, temporal lobe epilepsy and those with subdural evaluations were more likely to undergo Wada testing. We speculate that the emergence of alternative noninvasive language lateralization techniques, along with concerns about the reliability of results and awareness of complication risks, are major reasons for the decline.

Key words: epilepsy, surgery, seizures, temporal lobe, language, memory, Wada test
the decline of the intracarotid amobarbital test include shortages of sodium amobarbital, development of newer testing paradigms and noninvasive mapping techniques, as well as the risk of complications due to the invasive nature of the Wada test (Baxendale, 2009). The test has also been difficult to standardize across centres and there are concerns about the validity and reliability of the procedure. The aim of this study was to examine the incidence of the Wada test, and the clinical-decision making for or against Wada testing at a single surgical epilepsy centre.

Methods

We retrospectively reviewed all temporal lobe surgeries performed over a ten-year period (1997-2007) at the Cleveland Clinic Epilepsy Center. Data regarding patients’ age, surgical procedure, side of surgery, pathology, placement of subdural electrodes or depth electrodes, and utilization of the Wada test, were obtained. Statistical analyses were completed using SAS statistical software. The T-test was used to evaluate continuous variables, while the chi-square test was used to evaluate dichotomous variables. The study was approved by the Institutional Review Board.

Results

Patient Demographics

Seven hundred and seventy seven patients underwent temporal lobe surgeries between 1997 and 2007. The average age at presurgical evaluation was 31.7 years (range: 1-73 years) with a median age of 31 years. Four hundred and twenty seven (54.95%) patients had left hemispheric epilepsy. Hippocampal sclerosis was the most frequent pathological finding (42%). Additional pathological diagnoses are listed in table 1. Pathological results were not available for 16 patients. The mean age was 30.8 years (95% CI: 29.4-32.1 years) for patients with Wada testing compared to 31.6 (95% CI: 29.9-33.2) years for patients without Wada tests (not significant; p = 0.46).

Table 1. Pathological diagnoses after temporal lobe resection (n = 761).

<table>
<thead>
<tr>
<th>Pathology</th>
<th>N</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hippocampal sclerosis</td>
<td>322</td>
<td>42.3</td>
</tr>
<tr>
<td>Non-specific gliosis</td>
<td>198</td>
<td>26</td>
</tr>
<tr>
<td>Tumours</td>
<td>111</td>
<td>14.6</td>
</tr>
<tr>
<td>Malformations of cortical development</td>
<td>78</td>
<td>10.2</td>
</tr>
<tr>
<td>Vascular malformations</td>
<td>29</td>
<td>3.8</td>
</tr>
<tr>
<td>Strokes</td>
<td>21</td>
<td>2.8</td>
</tr>
<tr>
<td>Normal pathology</td>
<td>2</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Wada tests and laterality

Four hundred and ten Wada tests were performed on 52.8% of temporal lobe surgical patients. Wada test frequency in patients undergoing presurgical evaluation decreased over time based on the percentage of Wada tests per number of temporal lobectomies each year (figure 1). In 1997, 47 of 58 patients (81%) underwent Wada testing prior to surgery. In 2007, only 11 of 76 patients (14.5%) were tested. The difference in the number of Wada tests compared to the corresponding number of resections was significant when the testing time periods were dichotomized into 1997-2002 (n = 303) and 2003-2007 (n = 107) groups (χ² = 194.55, p > 0.0001). Of all patients with left temporal lobe epilepsies, 241 of 427 (56.4%) underwent Wada testing compared to 169 of 350 (48.3%) with right temporal epilepsies. Patients with left-sided epilepsy were significantly more likely to undergo Wada testing (χ² = 5.31; p < 0.05) than those with right-sided epilepsy. In 1997, 22/28 (78.6%) with right temporal and 25/30 (83.3%) with left temporal lobe epilepsy underwent a Wada test. In 2007 only 10/41 (24.4%) with left and 1/35 (2.8%) with right temporal lobe epilepsy resections underwent Wada testing (figure 1). The difference between Wada groups with left and right-sided pathology dichotomized into 1997-2002 (left: 159; right: 144) and 2003-2007 (left: 82; right: 25) time periods was statistically significant (χ² = 18.07, p < 0.0001).

Wada tests and invasive electrodes

A total of 123 patients with temporal lobe epilepsy underwent placement of subdural grids and strips to further localize or confirm the ictal onset zone and evaluate proximity to essential eloquent areas. Patients who underwent placement of subdural grids and strips were more likely to also undergo a Wada test (χ² = 6.64, p < 0.01). The effect was more pronounced in patients who underwent a Wada test and who had left-sided epilepsy (n = 59, 48%). This group was more likely to have subdural electrodes placed, compared to those with right-sided epilepsy and Wada testing (n = 19, χ² = 10.33, p < 0.001). Fifty-eight patients had only depth electrodes placed as part of the preoperative localization of the seizure onset zone. In contrast to patients undergoing placement of subdural electrodes, patients implanted with depth electrodes did not have a higher likelihood of being referred for Wada testing (χ² = 2.17, p = 0.14).

Surgery and Wada testing

The most common type of surgery performed in our cohort was anteromedial temporal lobe resection with removal of mesial structures (n = 461, 59.3%) followed by temporal lobe resection without mesial structure removal (n = 250, 32.2%). Further details regarding surgical intervention are...
Patients with left temporal lobe epilepsy and Wada testing were significantly more likely to undergo resection of the mesial temporal structures (n = 133, 32.7%) than those with right temporal lobe epilepsy and Wada testing (n = 112, 27.5%), p < 0.05 (χ² = 5.57).

**Discussion**

**Summary**

Our results indicate a decline in the utilization of Wada testing; a procedure which was performed in 1997 for the vast majority of patients with temporal lobe epilepsy and subsequently performed for only a few selected cases. Patients with a left-sided epileptogenic zone, and those patients undergoing subdural grid placement were more likely to be tested.

**Frequency in other studies**

In the early 1990s, Rausch et al. (1993) reported that nearly every epilepsy centre used Wada testing to lateralize language and memory in patients with intractable, surgically remediable epilepsy and that the Wada test was used in 85% of all surgical cases. In our study, we report a decline in the annual number of Wada testing

---

**Figure 1.** Incidence of left (A) and right (B) temporal lobe resections and Wada testing between 1997 and 2007.

**Table 2.** Types of surgical procedures (n = 777).

<table>
<thead>
<tr>
<th>Type of surgery</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anteromedial temporal lobectomy with resection of mesial structures</td>
<td>461</td>
<td>59.33</td>
</tr>
<tr>
<td>Selective amygdalo-hippocampectomy</td>
<td>31</td>
<td>3.99</td>
</tr>
<tr>
<td>Selective amygdalo-hippocamectomy, transcallosal procedure</td>
<td>5</td>
<td>0.64</td>
</tr>
<tr>
<td>Temporal lobe resection without removal of mesial structures</td>
<td>250</td>
<td>32.18</td>
</tr>
<tr>
<td>Subtemporal resection</td>
<td>3</td>
<td>0.38</td>
</tr>
<tr>
<td>Temporo-occipital resection with removal of mesial structures</td>
<td>1</td>
<td>0.13</td>
</tr>
<tr>
<td>Temporo-occipital resection without mesial structure removal</td>
<td>4</td>
<td>0.51</td>
</tr>
<tr>
<td>Posterior temporal lobe resection</td>
<td>21</td>
<td>2.7</td>
</tr>
<tr>
<td>No resection after craniotomy</td>
<td>1</td>
<td>0.12</td>
</tr>
</tbody>
</table>

listed in table 2. Patients with left temporal lobe epilepsy and Wada testing were significantly more likely to undergo resection of the mesial temporal structures (n = 133, 32.7%) than those with right temporal lobe epilepsy and Wada testing (n = 112, 27.5%), p < 0.05 (χ² = 5.57).
often in North America than in Europe (Baxendale et al., 2008). The Wada test was utilized significantly more in 252 epilepsy centres which participated in a recent survey (Gumnit, 2010). About 30% of respondents used the Wada test or used it rarely (defined as less than 25% of all cases). About 30% of respondents used the Wada test consistently or for more than 95% of all cases. The Wada test was utilized significantly more often in North America than in Europe (Baxendale et al., 2008). Haag et al. (2008) examined practice patterns regarding Wada testing by surveying 16 European epilepsy centres. The authors found that test frequency had decreased from 282 tests in 2000 to 210 tests in 2005. They also reported that the proportion of Wada testing in relation to the total number of resections was 38% (Haag et al., 2008). In our study, for the years 2005-2007, this proportion ranged between 10 and 35%. In line with our findings, Haag et al. (2008) also described a five-year decline in the proportion of resections to Wada tests from 56 to 35%.

Potential reasons for decline in Wada testing

There are several reasons for the current nadir in Wada testing. Development of alternative noninvasive assessment methods for speech and memory evaluation in patients with epilepsy has played a role. Baxendale and colleagues developed a predictive model of memory decline after temporal resection and found that memory decline (which occurred in a quarter of patients studied) could be detected by presurgical clinical characteristics including age and verbal IQ. These findings therefore detract from the predictive value of the Wada test with regard to postsurgical memory changes (Baxendale et al., 2006). The clinical use of fMRI (and emerging use of MEG) has become more widely available over the past decade (Abou-Khalil, 2007), although this procedure was not routinely used for our patients. At the Cleveland Clinic, the evaluation of patients who are candidates for epilepsy surgery using fMRI and MEG is a fairly recent development and it is not possible, therefore, to correlate Wada results from our cohort with the results from these newer investigations (Loddenkemper et al., 2009). In addition, the Wada is an invasive test with well documented risks for complications. A complication rate of up to 11%, including stroke and carotid dissection in up to 1% (Loddenkemper et al., 2008), has been reported. Furthermore, the validity and reliability of the Wada memory component are not well established. Simkins-Bullock (2000) examined the validity of the Wada test using well established epidemiological principles, and found only a paucity of data. Limited reproducibility of Wada test results on repeated studies has also been suggested (Loddenkemper et al., 2007). Furthermore, the Wada procedure remains a test that is difficult to standardize across centres given the variability of test stimuli, time of presentation, dosage and type of short-acting anaesthetic, and interpretation of results. Finally the last decade has seen limited availability of amobarbital. Several variations of the Wada test have been proposed including the replacement of amobarbital with methohexitol, propofol and etomidate, all with varying levels of success (Andelman et al., 2006; Jones-Gotman et al., 2005; Loddenkemper et al., 2009; Mikati et al., 2009). The evidence from the United States National Association of Epilepsy Centers suggests that financial reasons, especially reimbursement from third party payers, are not responsible for the decline of Wada testing frequency (Gumnit, 2010).

Indications

The Wada test, also called the intracarotid amobarbital procedure, was first introduced by Juhn Wada in the early 1950s, to lateralize language dominance in patients being evaluated for epilepsy surgery, primarily temporal lobe resections (Wada, 2008). Subsequently, following the case of a patient with epilepsy who underwent bitemporal lobectomy for refractory epilepsy with devastating memory loss, Branch et al. (1964) introduced the memory component to Wada testing. Although the Wada test has also been used to predict postsurgical seizure outcome as well as location of the ictal onset zone, these latter indications are rarely used today (Loddenkemper, 2008). Rarer indications of the Wada test include differentiating between primary and bilateral synchrony (Lombroso and Erba, 1970; Lombroso and Erba, 1969) as well as lateralization of mathematical skills (Delazer et al., 2005) and music abilities (Plenger et al., 1996). Today, few indications for Wada testing remain, and frequently risks of testing outweigh possible benefits. In an international survey, Baxendale et al. (2008) found that the primary indications for the Wada test remain lateralization of memory and language dominance. More than half the respondents were willing to consider assessing the risk of postsurgical amnesia without using the Wada test for temporal lobe
resection. Two thirds of respondents were willing to consider surgery without Wada data to lateralize speech. Resections of the language dominant hemisphere tend to be less extensive than resections on the non-dominant side (Baxendale et al., 2008).

Wada testing and language

In our study, we found that a higher proportion of patients with left-sided (presumably dominant hemisphere) epilepsy underwent the Wada test, compared to those with right-sided epilepsy, while patients with a left-sided epileptogenic zone were more likely to undergo a Wada test as well as subdural grid placement. The predominance of left sided Wada tests is likely due to the lateralization of language to the left hemisphere in the vast majority of patients (Snyder et al., 1990). Patients with left-sided epilepsies may also undergo more frequent placement of subdural grids, as grids allow for functional localization of language by direct stimulation. Furthermore, the use of grids implies that these patients appeared to have a more challenging clinical presentation which required intracranial confirmation of the epileptogenic zone within the temporal lobe and/or concurrent exploration of temporal and extratemporal areas in addition to functional mapping of adjacent eloquent cortex. Wada testing was more often used in patients with resection of mesial and lateral temporal structures, compared to resection of mesial structures only, in order to account for lateral and basal temporal language areas (Kim and Spencer, 2001).

Wada testing and memory

Recent evidence has obviated the need for Wada testing in determining memory lateralization. Based on multivariate regression analysis of 59 left temporal lobe resections in one study, Elshorst et al. (2009) found that Wada test memory scores were not a significant predictor of postoperative memory performance. In patients with conclusive data regarding memory lateralization based on either fMRI or magnetoencephalography, resection may be considered. In patients with inconclusive memory lateralization using these modalities or in patients with potential overlap between eloquent areas and the epileptogenic zone, subdural grid placement may be considered to provide additional information regarding memory location (Loddenkemper, 2008). Our findings suggest that patients with subdural grid placement were more likely to undergo Wada testing and those with left-sided epileptogenic zones were more likely to undergo Wada testing even with grid placement. In retrospect, this was likely due to possible overlap of eloquent areas, including memory and language, with the epileptogenic zone. This may also explain why the prevalence of Wada testing in patients monitored with depth electrodes was not significantly different for left and right-sided epilepsies.

Conclusion

The Wada is an invasive procedure with an appreciable complication rate as well as questionable validity and reliability. The emergence of a variety of noninvasive techniques has led to decreased utilization of Wada procedures. In current clinical practice the Wada test may be used when fMRI or MEG language assessment is inconclusive or not feasible (for example in patients with significant claustrophobia or implantable stimulators), and in those patients where a multimodal language assessment paradigm predicates the use of the Wada test. In most cases, however, the Wada test may be eliminated after counselling the patient of the risks of testing versus its potential benefit above and beyond other investigations and its limited predictive value in assessing postsurgical memory loss (Loddenkemper, 2008). We document the marked decline of and change in decision making for Wada testing in the presurgical evaluation of epilepsy patients over the last decade at a single centre.

Acknowledgments.
The authors acknowledge the contributions of Ranjani N Moorthi, MD, MPH, MS in completing statistical analyses for this manuscript. This manuscript was presented as a poster at the Annual Meeting of the American Epilepsy Society held at Boston in December 2009.

Disclosure.
None of the authors has any conflict of interest or financial support to disclose.

References


