

Presurgical Evaluation of Patients With Epilepsy: The Wada Test

Phoebe Wing-hei Leung^{1†}, Eric Chun-kwong Chung²

¹Resident, Department of Anaesthesiology & Operating Theatre Services, Queen Elizabeth Hospital, Hong Kong

²Associate Consultant, Department of Anaesthesiology, Queen Mary Hospital, Hong Kong

Edited by: Dr. Clara Ching-mei Poon, Honorary Clinical Associate Professor, the University of Hong Kong, Consultant, Department of Anaesthesiology, Queen Mary Hospital, Hong Kong; Guest editor: Dr. Lashmi Venkatraghavan, Associate Professor, University of Toronto, Director of Neuroanaesthesia, Department of Anaesthesia and Pain Medicine, Toronto Western Hospital, Canada

[†]Corresponding author e-mail: leungpwh93@gmail.com

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KEY POINTS

- The presurgical workup of a patient with epilepsy requires multidisciplinary input.
- The Wada test is primarily used for assessing hemispheric language and memory dominance to determine the feasibility of surgical resection.
- Understanding the principles of the Wada test enables anaesthesiologists to assist in the investigation and to anticipate possible perioperative challenges that the patient may encounter.
- There is no standardised protocol for the Wada test.
- The shortage of amobarbital has led to the use of other anaesthetics, such as propofol, etomidate and methohexital.
- With the advent of noninvasive imaging techniques, the need to perform the Wada test has been reduced to selected groups of patients for epilepsy surgery.

INTRODUCTION

Epilepsy is a common chronic neurological disorder characterised by recurrent seizures, and 30% of patients remain refractory to medical treatment.¹ Among refractory epilepsy, temporal lobe epilepsy (TLE) is an important subtype, as it is often associated with the most favourable surgical outcome. Surgical interventions, such as temporal lobectomy, serve as valuable treatment options for these patients to improve seizure control and quality of life. Comprehensive presurgical evaluation plays an integral role in the selection of surgical candidates and will generally involve a battery of imaging examinations, neurophysiological evaluations and neuropsychological assessments. The main objectives are to identify structural abnormalities and epileptogenic zones and to localise any functional neural tissues near the seizure foci. The feasibility of surgery is then determined, balancing the benefits of seizure control against the potential risks of inflicting major neurological deficits.

One of the diagnostic tests performed is the Wada test, during which an anaesthetic drug is selectively injected into each side of the brain to evaluate its individual language and memory functions. The test is offered to patients with technically resectable foci in the temporal lobe and provides information on potential postoperative functional deficit. Anaesthesiologists are involved in administering the anaesthetic drug and monitoring the patient during the Wada test.

With a particular focus on the Wada test, the aim of this review is to discuss the anaesthetic contributions to the multidisciplinary evaluation of patients for their potential candidacy for epilepsy surgery. Understanding the basic concepts of the Wada test is

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essential for anaesthesiologists to assist in the investigation and anticipate possible perioperative challenges the patient may encounter.

EPILEPSY SURGERY AND PRESURGICAL EVALUATION

Therapeutic epilepsy surgery encompasses curative resection and palliative intervention. Curative resection aims at the complete removal of epileptogenic zones responsible for triggering the seizures, without disrupting eloquent areas in the vicinity. Lesionectomy is an example in which focal, well-defined lesions are resected. Temporal lobectomy and selective amygdalohippocampectomy are options for TLE with lesions isolated to the temporal lobe, commonly arising from the hippocampus and amygdala.

Both disconnection surgery and neuromodulation are palliative procedures. Disconnection surgery mainly interrupts the nerve pathways that are thought to be involved in the spread of epileptic activity, whereas neuromodulation involves the use of an electrical device to alter nerve activity.

Presurgical evaluation requires multidisciplinary input from neurosurgeons, neurophysiologists, radiologists, anaesthesiologists, psychiatrists and clinical neuropsychologists. A series of diagnostic tests are performed (Table 1), and the information obtained provides insight into the epileptic processes, the cerebral organisation of cognitive skills and the safety of resection. This is relevant in the context of epilepsy surgery, because it is important to preserve the functional regions of the brain during the removal of the epileptogenic cortex, especially those eloquent areas responsible for language and memory. The decision to perform surgery is thus a balance of achieving seizure control, the projected risk of inducing unacceptable cognitive and neurological deficit from surgery.

THE WADA TEST

The Wada test, also known as the intracarotid amobarbital test, is named after Juhn Atsushi Wada, a Japanese neurologist. The test was initially developed to study the language and memory side effects of electroconvulsive therapy. In the late 1940s, it was incorporated into the preoperative evaluation for cerebral language dominance in epilepsy surgery. The test was later extended to the assessment of hemispheric memory function in the 1960s.³ Nowadays, it is indicated for the assessment of language dominance and memory capacity in patients planned for the resection of temporal lobe structures.

Technique

During Wada testing, each cerebral hemisphere is transiently inactivated by injecting a small dose of anaesthetic into the respective supplying internal carotid artery. The capacity of each hemisphere to support language and memory function can then be assessed. This information helps to predict postoperative cognitive deficits and inform risk-benefit discussions when surgical resection is an option.

Objective	Examples
1. Identification of structural abnormalities	<ul style="list-style-type: none"> • Magnetic resonance imaging (MRI) • Computed tomography (CT)
2. Localisation of the epileptogenic zone(s)	<ul style="list-style-type: none"> • Noninvasive electroencephalogram (EEG) • Video EEG • Invasive EEG (intraoperative electrocorticography [ECoG] using intracranial subdural grid/strip and/or depth electrodes) • Functional MRI (fMRI) • Single-photon emission CT (SPECT) • Magnetoencephalography (MEG)
3. Mapping of cortical functional areas	<ul style="list-style-type: none"> • Functional MRI (fMRI) • Positron emission tomography (PET) • MEG • ECoG
4. Detection of functional deficit	<ul style="list-style-type: none"> • Wada test • SPECT • PET • MEG

Table 1. Examples of Diagnostic Tests Done as Part of the Presurgical Evaluation (Adapted from Baumgartner et al²)

There is no standardised protocol, and the practice varies among centres. The variability ranges from the choice of drug, the dose used, the rate of infusion, the side tested first, the tools for testing memory and language and the methods of scoring. Commonly, the test is started on the presumed side of surgery and then repeated on the contralateral side.

On the day, the patient is brought to the radiology suite with bilateral electroencephalogram (EEG) electrodes attached to the scalp. (Figure 1) Simultaneous EEG recordings is essential to assess the onset and offset of the anaesthetic drug effect and to detect any seizure activity during the procedure.

Before the testing begins, a neuroradiologist performs a cerebral angiogram. (Figure 2) The femoral artery is punctured after local anaesthesia, and a catheter is advanced into the internal carotid arteries under fluoroscopic guidance. With the catheter positioned just distal to the origin of the internal carotid artery, an angiogram is performed to visualise the cerebral vascular pattern and to exclude any anomalies. A persistent trigeminal artery should be ruled out due to the concern of inadvertently



Figure 1. Bilateral electroencephalogram scalp electrodes.



Figure 2. Cerebral angiogram.

anaesthetising the brainstem. Other vascular variations, such as significant interhemispheric cross-flow or alternative supply of the posterior cerebral artery via the posterior communicating artery, may influence the results.

After the angiogram, the anaesthesiologist administers the anaesthetic drug. Prior to the injection, the patient is asked to raise both arms in the air and spread the fingers while counting out loud. Paralysis of the contralateral arm occurs as the drug is being delivered. A neurologist monitors the EEG and confirms the efficacy of hemispheric inactivation. Subsequently, a neuropsychologist performs visual, speech and memory assessments. After completing the first side, the patient should be allowed some time to recover prior to testing the other side. The time taken would depend on the anaesthetic drug used.

Language Testing

To test various components of language, the patient will be presented with tasks, such as naming objects, reading and repeating sentences. Although most healthy, right-handed individuals are left-hemisphere dominant for language, patients with epilepsy have a higher likelihood of atypical language representation. This is particularly true for those with a left-sided seizure focus, and they may present with bilateral or right-lateralised language dominance. Factors such as the age of seizure onset, the location of seizure focus and handedness may all contribute to cerebral reorganisation and developmental shift in language dominance.^{4,5}

Memory Testing

A series of items will be shown to the patient for subsequent recall. (Figure 3) The result of the assessment would reflect the memory capacity of the contralateral, “lucid” hemisphere unaffected by anaesthetics. Once the effect of the drug has dissipated, as reflected by the return of muscle tone and normal EEG, the previously displayed items are presented for recognition. Different centres have different protocols on what is considered a “pass,” and it can be based on the absolute number of correct items or the difference between each hemisphere’s performance.

Two theories have been described to explain hippocampal function in processing memory: functional reserve versus functional adequacy.⁶ Anaesthetising the epileptogenic hemisphere tests the functional reserve of the contralateral temporal lobe, that is,



Figure 3. Language testing.

its capacity to support memory after surgery. Poor performance would predict memory impairment after resection. On the contrary, anaesthetising the contralateral side tests the functional adequacy of the epileptogenic hemisphere, and this usually elicits defective memory performance owing to the functional deficit of the diseased temporal lobe. If the epileptogenic hemisphere is found to support considerable memory function, a more significant memory decline would be expected. In the case of left TLE, reduced functional reserve of the nonepileptogenic hemisphere and high functional adequacy of the epileptogenic hemisphere would suggest a major risk for postoperative memory decline.

Drug Choice

The intracarotid administration of anaesthetic drugs presents unique pharmacokinetic challenges as the intra-arterial dose required is much less than the intravenous dose, and this generally does not vary with the patient's weight.

The standard drug used for the Wada test is sodium amobarbital, which is a barbiturate with low toxicity and short duration of action. However, its worldwide shortage has led to the exploration of various anaesthetics. Ideally, such drug should possess rapid onset and offset of action, low toxicity and low epileptogenic potential. Furthermore, it should produce consistent clinical and electrophysiological effects while causing minimal residual disturbance in consciousness to allow multiple testing in a single session.

Methohexital, pentobarbital, propofol and etomidate have all been investigated as substitutes (Table 2).⁷⁻¹⁰

Potential Complications

One case series documented an overall complication rate of 10.9%.¹⁴ Neurologic complications include seizure, intracranial vessel injury, carotid artery dissection, arterial vasospasm with or without transient deficits, stroke and transient encephalopathy.^{14,15} Examples of nonneurologic complications are contrast reactions, contrast-induced nephropathy and haematoma at the puncture sites. Transient symptoms related to anaesthetic injection are also common, ranging from myriad physical symptoms to a change in mental state. Inadvertent reflux of the anaesthetic drug into the basilar artery during posterior cerebral artery injection can cause respiratory arrest and loss of consciousness.

Drug (Concentration)	Structure	Dose (Adults)	Remarks	Disadvantages
Amobarbital (25 mg/mL)	Barbiturate	75-125 mg, followed by 25 mg	Gold standard; short acting; low toxicity; extensive clinical experience	Successive injections need to be separated by at least 45 min to allow time for electrographic recovery, which may limit the number of procedures that can be done in a day. ¹¹
Methohexital (1 mg/mL)	Barbiturate	3 mg followed by 2 mg	Short acting; multiple boluses needed	Increased risk of seizures ¹² Not widely available
Pentobarbital (2 mg/mL)	Barbiturate	20-24 mg followed by 12-16 mg	Longer duration of action than methohexital but shorter than amobarbital; does not always require additional injection	Side effects (eg, drowsiness, confusion)
Propofol (1 mg/mL)	Nonbarbiturate	10-20 mg	Short acting; multiple boluses needed	Side effects (eg, hypotension, confusion, increased muscle tone, twitching) ¹³ Lipid emulsion may cause pain and discomfort on injection
Etomidate (2 mg/mL)	Nonbarbiturate; imidazole derivative	2-mg bolus followed by an infusion of 6 mL/h (12 mg/h)	Minimal haemodynamic effects; short acting; infusion required to maintain anaesthesia	Infusion pump needed; side effects (eg, shivering, myoclonic movements, dystonic posturing) Dose-dependent cumulative suppressive effect on adrenal function

Table 2. Drugs for the Wada Test

Limitations

There are several limitations of the Wada test. First, it solely examines lateralisation without functional localisation within each hemisphere. Second, the hippocampus is perfused by branches from both the middle and posterior cerebral arteries, and variable vascularisation may affect the distribution of anaesthetic agents. Third, drug administered via the internal carotid artery causing widespread inactivation of the cortex may lead to aphasia, which may interfere with memory testing. Therefore, a superselective Wada test has been developed, targeting an arterial branch that supplies a specific functional and anatomical region in the brain. For instance, posterior cerebral artery injection inactivates the posterior portion of the hippocampus and adjacent mesial temporal lobe structures, with minimal effects on language.¹⁶

ANAESTHETIC MANAGEMENT OF WADA TESTING AND CURRENT ROLE OF WADA TESTING

The anaesthetic management of Wada testing is summarised in Table 3. The Wada test's invasive nature precludes its routine use in the evaluation of epilepsy surgical candidates, especially when the results of other noninvasive tests are considered

Stage	Steps
Preoperative	<p>Patient assessment</p> <p>Preanaesthetic assessment requires a complete history of the patient's medical condition and physical status, followed by a thorough assessment of his or her ability to cooperate throughout the test and the presence of any features suggesting obstructive sleep apnoea and difficult airway. The history of renal impairment, as well as allergy to iodine, shellfish or contrast should be ascertained. Other pertinent information includes the patient's epilepsy status, the type and frequency of seizures, the use of antiepileptic medications and their related side effects. Furthermore, the presence of any psychiatric comorbidity is important as it is frequently found in patients with epilepsy,¹⁷ and psychiatric symptoms may be aggravated during the perioperative period.</p> <p>Patient preparation</p> <p>The procedure should be explained to the patient in advance to facilitate patient preparation and to minimise his or her anxiety. Safety issues and transient neurologic effects caused by the anaesthetic drug should be explained. Usual fasting recommendations should be observed. Patients should continue their usual antiepileptic medications, and sedative premedication is best avoided.</p>
Intraoperative	<p>Anaesthesiologists play an essential role in monitoring and ensuring patient safety while facilitating the test. During the test, the patient is positioned supine with peripheral venous access secured. Standard monitoring, which consists of heart rate, blood pressure, respiratory rate, electrocardiogram, pulse oximetry and capnography, should be available. The pulse oximetry probe may be placed on the lower limb, and blood pressure measurements may be temporarily withheld during the test to minimise interference and distraction from the tasks. Temperature control is essential, as the test can be long and angiography suites are typically cold. An underbody warming device may be useful to avoid interfering with groin puncture and testing. In addition, a urinary catheter may be considered if longer procedural time is expected, taking into account the higher volume of endovascular flush and the diuretic effect of contrast.</p> <p>The internal volume of the intra-arterial catheter and extension lines should be carefully noted so that a precise volume and dose can be administered to achieve unilateral anaesthesia without global obtundation. Drug boluses should be given slowly. Additional boluses or infusion may be required to maintain the anaesthetic effect for sufficient testing. Hence, coordination within the multidisciplinary team is very important. The catheter should not be flushed during anaesthetic administration or at the end of the test to avoid inadvertently administering excess anaesthetic. Any anaesthetic agent within the catheter dead space should be aspirated before catheter flushing or further imaging.</p> <p>The use of heparin for thromboembolic prophylaxis varies with institutional practices. The anti-thrombin effects of heparin can be monitored by measuring the activated clotting time and can be reversed with protamine if necessary.</p> <p>The patient should be closely monitored for the occurrence of seizures and haemodynamic instability. Transient shivering and muscle twitching during the test are common. Emotional instability and behavioural disturbances infrequently occur.⁹</p>
Postoperative	<p>A postanaesthesia care facility should be available for haemodynamic and neurologic monitoring.</p>

Table 3. Perioperative Management of Patients Undergoing the Wada Test

adequate for treatment decisions. Functional magnetic resonance imaging (fMRI), being a noninvasive alternative, is increasingly used to assess cerebral language and memory dominance. It has high concordance with the Wada test in subjects with clear left lateralisation and is capable of replacing the Wada test in determining language dominance. However, this method is less sensitive for bilateral or atypical language representation.^{18–20} On the other hand, there have been attempts to measure the lateralisation of material-specific memory using various fMRI paradigms. Yet, the concordance between fMRI and the Wada test for memory lateralisation has been less consistent.^{21,22}

To date, a highly specific and clinically applicable fMRI protocol that can reliably predict postsurgical outcomes has not yet been established. Therefore, some centres still choose to perform the Wada test in selected groups of patients who are at risk of postoperative global amnesia or when their imaging results on language and memory lateralisation are inconclusive or atypical. One must note that fMRI and Wada testing are fundamentally different: the former is an activation study, whereas the latter is a suppressive method that tests the ability of one hemisphere to sustain a function without influence from another.

WADA TESTING IN PAEDIATRIC PATIENTS

Performing the Wada test with children presents a special challenge, as it requires a long period of concentration and cooperation. Moreover, many of these patients are cognitively impaired. The setting and procedure may be particularly stressful for them, and they may become agitated, especially during femoral arterial cannulation, increasing the risk of femoral artery injury. Sedation may be required, and the use of propofol²³ and dexmedetomidine²⁴ for angiography has been reported. The child's ability to cooperate for testing must be carefully assessed, as an uncooperative child not being able to complete the test will not only fail to provide memory and language information but also subject the child to the potential harms of angiography as outlined above.

CONCLUSION

Presurgical planning for patients with temporal lobe epilepsy requires the close collaboration of multiple specialties. Despite the recent drive to replace it with noninvasive techniques, the Wada test remains a useful instrument in selected candidates for assessing cerebral dominance and predicting postoperative cognitive decline. Understanding the principles of the Wada test is essential for anaesthesiologists to facilitate the procedure and prepare for any perioperative challenges and neurocognitive risks that the patient may encounter.

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