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Reliability and safety of Etomidate speech test in children with drug resistant focal epilepsy

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ABSTRACT

Purpose: To review our experience with the Etomidate speech test (EST) for lateralizing language in children undergoing epilepsy surgery evaluation

Methods: This retrospective study included children (< 18 years) with drug refractory focal epilepsy undergoing EST for bilateral or poorly reliable language representation on functional MRI. Data for consecutive children who underwent EST between January 2013 to June 2017 were reviewed.

Results: Twenty-one children (mean age at EST, 13.1 ± 4.4 years) were studied, with 19-right hemispheric and 20 left hemispheric injections. Six patients had neurological co-morbidities. Duration of ipsilateral EEG slowing was sufficient for speech testing in all children with a single bolus of Etomidate per carotid artery. Language was lateralized to one hemisphere in 17 (80.9%) and bilateral in two cases. EST was unsuccessful in two patients because of diffuse EEG slowing. Contralateral transient frontal EEG slowing was seen in 14 (73.7%) cases. EST was well tolerated in all the patients.

Conclusions: The EST was found to be successful and safe in lateralizing language in most of our drug refractory pediatric epilepsy cohort.

1. Introduction

Since its description 70 years ago (Wada, 1949), the Wada test continues to be the gold standard for language lateralization in patients undergoing epilepsy surgery evaluation. In more recent years, multiple non-invasive techniques have evolved for language lateralization including functional MRI, magnetoencephalography and transcranial magnetic stimulation, and the required expertise is gradually developing (Papanicolaou et al., 2014). These techniques have demonstrated good concordance with the Wada test. A meta-analysis of 22 adult studies (Bauer et al., 2014) showed 19.5% discordance between the results of Wada and fMRI for preoperative language lateralization. Also major discordance was seen (51%) with an atypical language representation.

Therefore, despite limitations such as its invasive nature, patient discomfort, requirement for patient cooperation, need for a neuro-interventional set-up, availability of limited time to perform speech tests and problems of cross-flow, the Wada test continues to be used in various epilepsy surgery centers across the world. Wada test is therefore recommended by ILAE where fMRI shows atypical language dominance (Jayakar et al., 2014).

Irregular and unreliable availability of amobarbital worldwide has led various epilepsy centers to explore alternative agents for Wada test like methohexital, pentobarbital, etomidate and propofol (Patel et al., 2011).Etomidate is a potent non-barbiturate agent with rapid onset and short duration of action with minimal hemodynamic effects.(Giese and Stanley, 1983) Use of etomidate in the Wada test was first described in Montreal.(Jones-Gotman et al., 2005) Subsequent reports, based

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predominantly on experience with adult patients, have used both "bolus followed by infusion"(Jones-Gotman et al., 2009; Mariappan et al., 2013) and "bolus alone" protocols,(Andelman et al., 2013; Passarelli et al., 2014). This retrospective study aimed to evaluate our experience with the "bolus injection alone" etomidate speech test (EST) in children with focal drug-resistant epilepsy (DRE) undergoing epilepsy surgery (ES) evaluation with predominant bilateral language representation on fMRI.

2. Methods

This retrospective study was approved by the Ethics Board of the Hospital for Sick Children (eREB no. 1000057127). The electronic records of consecutive children below 18 years of age with drug refractory epilepsy (undergoing epilepsy surgery evaluation at The Hospital for Sick Children, Toronto) with bilateral or poorly reliable language representation on fMRI, who underwent etomidate speech testing (EST) for language lateralization between January 2013 and June 2017, were reviewed. The data was extracted using a pre-designed data abstraction form (demographics, details of epilepsy and pre-surgical work up, details of etomidate speech test, surgery performed, seizure outcome at last visit, language deficits).

2.1. Etomidate speech test

The patient arrived on the ward on the morning of the test. The patients practiced the speech tests with the neuropsychologists before they went to the interventional radiology suite. The practice test items and the actual items for the two hemispheres were identical. EEG electrodes were then placed. Twenty-one channels were recorded, including the 19 standard scalp electrodes, referenced to Pz-prime (1 cm posterior to Pz in midline). The EEG was sampled at 256 Hz with a low frequency filter at 1 Hz and high frequency filter at 70 Hz. The scalp EEG was then displayed in a bipolar antero-posterior montage (Natus Neuroworks software). EEG tracing was reviewed continuously before, during and after the EST. Patients were also monitored with ECG, noninvasive blood pressure monitoring and pulse oximetry.

The procedure was performed by an interventional neuroradiologist in a biplane neuroangiography suite (Artis Q, Siemens Healthineers). All procedures were performed through common femoral arterial access, after infiltration of 1% lidocaine for local anesthesia, with light sedation and/or anxiolysis provided if required during the arterial access. Systemic heparinization was not routinely used, given the short procedure duration. However, catheters were maintained on forward flush with heparinized saline pressurized above systemic arterial pressure. Cerebral angiography was performed through a 4Fr diagnostic catheter positioned in the high cervical internal carotid artery, obtaining anteroposterior and lateral projections to confirm catheter position and exclude variant anatomy (e.g. persistent carotid-basilar anastomosis).

Before injection, a baseline EEG visual field and hand strength were obtained. When the patient was ready, a 0.03–0.04 mg/kg bolus dose (2 mg/ml vial, maximum dose 2 mg) (Jones-Gotman et al., 2005) of undiluted etomidate was administered over 30 s through the internal carotid artery. Our center does not use etomidate infusion as "bolus alone" was shown to be better tolerated by Andelman et al. (2013). Further, we only perform speech testing during the Wada test and this negates the requirement for infusion.

The patient would count at the time of injection, and the speech tests were initiated once there was an onset of ipsilateral hemispheric EEG slowing and loss of contralateral hand strength. After the testing of one hemisphere, the team waited till the EEG returned to baseline (usually 5–10 min) before injecting an identical dose in the other hemisphere. Usually, the hemisphere with the epileptogenic lesion was injected first. Recovery from the sedation was then ensured by the clinical neuropsychologist and absence of slowing on EEG.

2.2. Language/speech tests

The language protocol was individualized to each child, taking into consideration the child's age, developmental level, and language ability, as determined by the prior neuropsychological assessment. Only items completed at 100% accuracy were used in the test. Baseline testing was carried out prior to injection in order to compare performance to that when the drug was circulating. Whenever possible, the child was asked to count at the time of the injection, and this was followed by tests of naming pictures and/or objects. Spelling, reading, and/or reciting the days of the week or the alphabet, were also assessed when the child was capable of such tasks. Comprehension was assessed by asking the child to respond to simple commands. EEG monitoring for the presence of slow waves, as well as paralysis on the side contralateral to the injected hemisphere were taken as indicators that the injection was successful.

Following the injection, indications of speech representation within the hemisphere were speech arrest and/or errors on tasks the child was capable of performing perfectly at baseline. For interpretation, we used the previously described method (Saltzman-Benaiah et al., 2003). Unilateral representation was determined when injection of one hemisphere did not interrupt language, but injection of the other hemisphere did. When injections to both hemisphere were done and deemed successful, a patient was classified as having bilateral speech representation if she/he demonstrated at least one of the following: (a) no speech arrest or errors when either of the hemispheres was injected (i.e. duplication of speech representation), (b) a similar number of errors and of comparable levels following injection of either hemisphere (i.e. speech representation shared between the hemispheres) or (c) a qualitatively different pattern of speech errors following injection of either hemisphere (i.e. speech specialization distributed between the hemisphere.

2.3. Statistical methods

Descriptive statistics (mean/standard deviations/range/median/inter-quartile range/percentages) were used to describe the results. Data compilation was performed using Microsoft Excel 2010 (Microsoft, Redmond, Wash., USA). STATA 9.0 was used for data analysis.

3. Results

A total of 172 functional MRI studies were done for language lateralization during the study period. Out of these, 21 patients (12.2%) had bilateral or inconclusive results for language lateralization on fMRI requiring further investigation with the EST. Fifteen patients (71.4%) were right-handed. There were 19 injections in the right and 20 injections in the left hemisphere. Three patients who had unilateral injection were right handed and had an epileptogenic lesion in the right hemisphere. Injection into the right hemisphere caused no speech deficits and an assumption of left hemispheric lateralization of language was made. In these isolated cases the decision was based on the discretion of treating neurologist.

The mean age at the EST was 13.1 years (standard deviation 4.4 years; range 4–18 years). Although three patients had co-morbid intellectual disability, one had learning disability and two had inattention and hyperactivity, the EST test could be done successfully after test modifications by clinical neuropsychologists. 23% of our cohort was left handed and 4% (one patient) had no clear handedness. Other clinical characteristics of the study population are summarized in Table 1.

The mean dose of etomidate was 1.74 mg in the right injections and 1.65 mg in the left injections. The mean onset of ipsilateral EEG hemispheric slowing after injection was 12.8 s on the right side and 14.8 s on the left side. The ipsilateral continuous hemispheric slowing lasted for a mean of 278.7 s on the right and 278.5 s on the left side. This duration was enough for the adequate completion of speech testing

Table 1
Characteristics of the study participants.

Characteristic	N = 21
Mean age at onset of seizures in years, SD (range)	8.65, 4.74 (0.7 to 16 years)
Mean age at Etomidate speech test in years, SD (range)	13.1, 4.43 (4 to 18 years)
Mean age at surgery in years(n = 14), SD (range)	13.99, 3.94 (5 to 19 years)
Sex, Females, n (%)	10 (47.62)
Handedness, n (%)	
Right	15 (71.43)
Left	5 (23.81)
Indeterminate	1 (4.76)
Seizure frequency (1 month prior to EST), n (%)	
Daily	5 (24%)
Weekly	8 (38%)
Monthly	8 (38%)
Mean number of AEDs tried prior to EST, SD	3, 1.27
Number of patients on Topiramate at the time of EST, n (%)	4 (19%)
Etiology, (n)	
Focal cortical dysplasia (FCD)	43%(n = 9)
FCD2A	3
FCD1	1
Suspected FCD	5
Tumors	19%(n = 4)
DNET	1
Low grade astrocytoma	1
Glioma	1
Pleomorphic xanthoastrocytoma	1
Tuberous Sclerosis	1
Polymicrogyria	1
Gliosis	2
Ischemic stroke	1
Mesial temporal sclerosis	1
Oligodendrogliosis	2
Type of surgery performed (n = 14)	
Temporal lobectomy	5 (4 left, 1 right)
Focal tailored resection	4 (2 right, 2 left; 3 frontal, 1 temporal)
Multilobar corticectomy	3 (2 left, 1 right)
Lesionectomy	2 (1 left, 1 right)
Mean follow up period for patients who underwent surgery in years (n = 14), SD	0.95, 0.86 (Median 0.60)
ILAE Surgical outcomes (N = 14)	
Class 1	10 (70%)
Class 2	1
Class 4	1
Class 5	2

AED-Anti-epileptic drug; DNET, Dysembryoplastic Neuro-Epithelial Tumour; EST-Etomidate Speech Test; FCD-Focal Cortical Dysplasia; ILAE – International League against Epilepsy; SD-Standard deviation.

in all patients (Table 2). None of the patients required additional injections due to inadequate EEG slowing or incomplete paralysis. Contralateral EEG slowing (Fig. 1) was noted in 14/19 (73.7%) patients with right injections (11 frontal, 3 diffuse) and 16/20 (80%) patients with left injections (11 frontal, 5 diffuse). It was transient or brief and intermittent in most cases (except two) and allowed for successful completion of the test. However, in two cases (aged 5 years and 14 years), the contralateral slowing was diffuse and persisted, resulting in failure of testing. Angiogram of these patients did not show any abnormalities to account for diffuse slowing. Enhanced inter-ictal epileptiform discharges after etomidate injection was noted in three patients. Motor paralysis was clearly contralateral in these cases.

Of the 19 cases with successful testing, the EST lateralized language to one hemisphere in 17 cases (80.9%; 95% confidence interval, 58.1%–94.6%). The left hemisphere was the language-dominant hemisphere in 13 cases (all had complete aphasia with preserved attention and cooperation). Right hemisphere was language dominant in four cases (3 had complete aphasia [with preserved attention and cooperation] and one had impaired receptive language dysfunction with

Table 2
Results of Etomidate speech test in the study population.

Characteristic	N = 21
Mean dose of etomidate per injection in milligrams, SD	
Right sided (n = 19)	1.74, 0.40 (Median 2)
Left sided (n = 20)	1.65, 0.52 (Median 2)
Mean latency of onset of hemispheric slowing in seconds, SD	
Right	12.82, 11.58 (Median 11)
Left	14.85, 9.70 (Median 12.50)
Mean duration of hemispheric slowing in seconds, SD	
Right	278.74, 104.84 (Median 254)
Left	278.50, 104.47 (Median 258.50)
Patients with contralateral slowing, n	
Right sided injection	14 (11 frontal, 3 diffuse)
Left sided injection	16 (11 frontal, 5 diffuse)
Adverse effects of Etomidate speech test	
Inappropriate emotional reaction	4
Habitual seizure	1
Ipsilateral posturing and eye deviation (no ictal EEG change)	1
Yawning	1
Shivering	1
Itchy and tired	1

SD-Standard deviation.

no interruption of speech on left sided injection). The language representation was bilateral in two cases and two patients failed the test due to diffuse slowing. Further sub analysis on five (23%) left handed subjects showed right hemispheric dominance in 2/5 (40%) and bilateral language 2/5 (40%) and one child (20%) failed the test.

The EST was well tolerated in all the patients. The most common adverse effect noted was inappropriate emotional reactions like crying or laughing (4 children). One child became very sleepy after the initial one-side full dose etomidate injection; the subsequent injection was done with smaller multiple boluses with subsequent successful speech testing. Ipsilateral posturing and eye deviation were seen in one child with no ictal EEG change. One child developed one habitual seizure 10 min after the completion of the etomidate speech test. Other less reported adverse effects included yawning (1), shivering (1) and "feeling itchy and tired" (1). There were no vascular/systemic complications of angiography.

Fourteen patients proceeded to undergoing subsequent epilepsy surgery. The reasons for "no surgery" included involvement of language dominant hemisphere (n = 5), surgery found inappropriate after invasive EEG monitoring (n = 1), and family refusal for surgery (n = 1). Ten patients (71.4%) had ILAE seizure outcome 1 after a mean follow up of 0.95 years. Only 1 patient had language deficit (word finding difficulty and hesitation) on follow up after surgery. This patient had left hemisphere dominant language on EST and bilateral language representation on fMRI and had underwent right posterior-temporal cortical resection.

4. Discussion

This retrospective study in children demonstrated that the EST (bolus only) successfully lateralized language to one hemisphere in 81%, where fMRI was inconclusive or bilateral. EST was unsuccessful in two cases because of diffuse EEG slowing. It was well tolerated in all patients with only minor adverse effects. Only one patient developed post-operative language deficits despite a favorable EST result which could be suggestive of more complex language network in pediatric epilepsy patients as previously reported by Heinz et al (1994). Their group compared intracarotid amytal test (WADA)with intraoperative language mapping and emphasized that very young children may

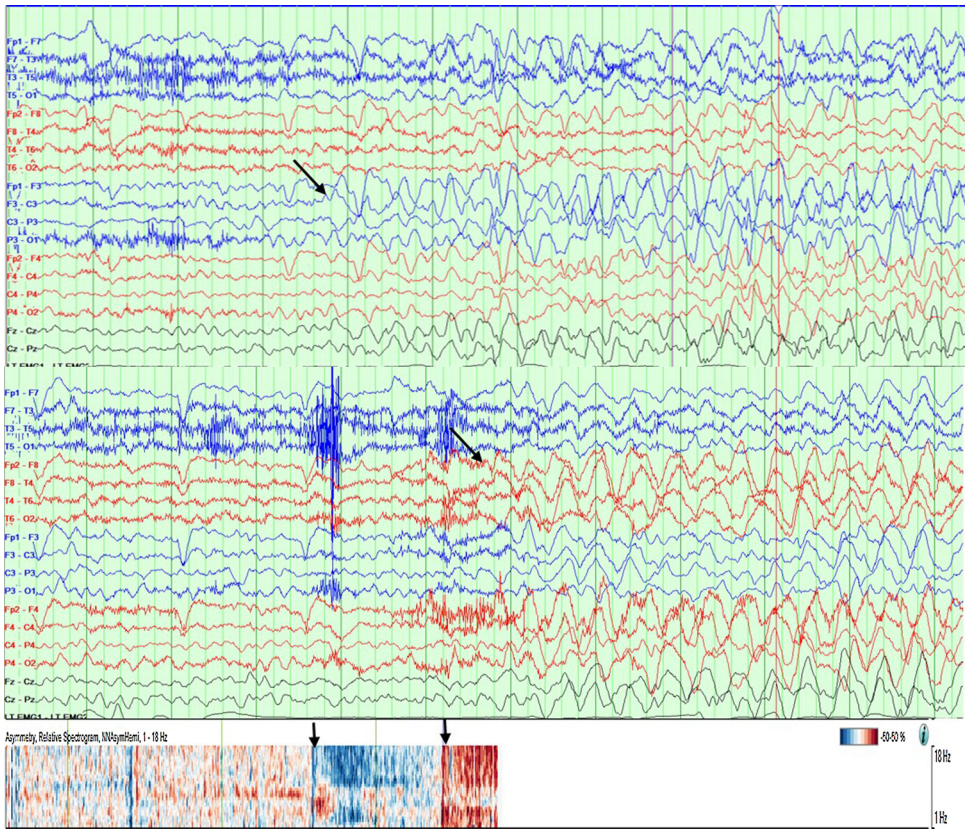

Fig. 1. Extracts from the EEG recording during Etomidate Speech Test. EEG (A) shows sudden onset 2–4 Hz delta/theta activity (initially polymorphic and then more rhythmic) over the left hemisphere after left injection (intermittent mainly frontal slowing over right hemisphere as well) and similar activity over right hemisphere (intermittent diffuse slowing over left hemisphere as well) after right injection (B). [Low frequency filter 1 Hz, high frequency filter 70 Hz, notch filter 60 Hz, sensitivity 10 μV/mm, timebase 30 mm/sec, sampling rate 256 Hz]. Asymmetry - Relative Spectrogram (Persyst software, AZ, USA) is shown in C. "x" axis is time (2 h per page), "y" axis is frequency of the EEG activity (1–18 Hz) and the "colour" code denotes the hemisphere: blue represents left hemispheric activity and red color represents right hemispheric activity. It shows predominant blue colour after left hemispheric injection and then predominant red colour after right sided injection, indicating higher amplitude respective hemispheric activity across all frequencies. (The patient was a 13 year old boy with left temporal lesion (query Focal cortical dysplasia type 1) with drug-resistant focal epilepsy. Positron Emission tomography was concordant. EEG indicated left temporal seizure onset. Functional MRI brain showed bilateral language representation. Etomidate speech test also showed bilateral language representation. Neuropsychology assessment indicated weak memory. He underwent language sparing left anterior temporal lobectomy. He was seizure free after surgery with no language deficits.

transfer language to contralateral hemispheric regions even after they have started to talk and form sentences especially when right hemispheric dominance of language is suspected.

Jones-Gotman et al (Jones-Gotman et al., 2005) first described using etomidate in the Wada test in adults in 2005. They used a bolus etomidate injection followed by infusion to complete language and memory tasks. It was found to be a viable alternative to amobarbital. Andelman et al., 2013 subsequently described successful use of bolus injections alone for memory testing in adults. They described seizures, severe obtundation and severe tremor/myoclonus with continuous infusions. (Passarelli et al., 2014) also described use of bolus injections for memory and speech testing in 54 adults. However, 10.7% patients required additional bolus injections to complete the testing. We used only bolus etomidate injection in children and found it sufficient for language testing. Language could be lateralized to one hemisphere in 80.9% cases.

Onset of ipsilateral EEG slowing has been described to be 30–39 seconds after the bolus injection.(Jones-Gotman et al., 2005; Mariappan et al., 2013) We noted such slowing after a mean of 12.8–14.8 seconds in our study population. The duration of total slowing was enough to complete the language/speech tests. We also noted contralateral slowing in 30/39 (77%) cases. Contralateral slowing in our cohort was mainly frontal and short lived and did not affect the interpretation of the test results. Jones-Gotman et al. (2005) described contralateral slowing in 75% cases. However, Mariappan et al. (2013) noted this in only 31% cases.

Accentuation of inter-ictal epileptiform abnormalities have been described in up to 70% cases.(Mariappan et al., 2013) It is usually seen on the hemisphere with epileptogenic lesion. We found increased inter-ictal epileptiform abnormalities in 3/21 patients. This could be explained from short action of the bolus injection with no concurrent use of etomidate infusion in our cohort. Etomidate is known to activate epileptiform abnormalities including high frequency oscillations. (Rampp et al., 2014) We also observed one habitual seizure 10 min after the etomidate injection in one patient (baseline seizure frequency was weekly to monthly), which was possibly related to etomidate administration. Andelman et al. (2013) described seizure in one patient during Wada test using etomidate infusion. Other series have not reported any seizures with etomidate. (Jones-Gotman et al., 2005; Passarelli et al., 2014) However, etomidate has been even used to induce seizures to localize the epileptic area in patients with temporal lobe epilepsy (Pastor et al., 2010).

Etomidate is otherwise well tolerated and shivering is described as the most common adverse effect, seen in up to 50% cases. (Jones-Gotman et al., 2005; Mariappan et al., 2013). Shivering was noted only in one patient and most common adverse reaction was inappropriate emotional reaction, seen in 4 children (19%). A previous study reported similar mood changes with etomidate use in 23% cases. (Mariappan et al., 2013). We observed only minor adverse effects which did not interfere with the speech testing. Additionally, there were no complications related to femoral access or carotid catheterization in our cohort.

To our knowledge this is the largest retrospective pediatric study analyzing the safety and efficacy of EST. The limitations of the study were retrospective data collection and the small sample size. We also did not compare Wada with sodium amytal to Wada with etomidate. We conclude that EST was found to be successful and safe in lateralizing language with bolus injections in majority of our pediatric cohort with drug-resistant epilepsy where fMRI was inconclusive or bilateral. A more careful review of the fMRI and Wada test results would help us to improve the imaging parameters and language testing paradigms. This may improve the success rates of a non-invasive test like fMRI for language lateralization at our center in future.

Conflicts of interests

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