CHAPTER 5

CHAPTER 5

The intracarotid amobarbital or Wada test: unilateral or bilateral?

SG Uijl

FSS Leijten

JBAM Arends

J Parra

AC van Huffelen

PC van Rijen

KGM Moons

Submitted 2007.

Abstract

Purpose. In the Netherlands, presurgical screening for temporal lobe epilepsy (TLE) includes the intracarotid amobarbital procedure (IAP), consisting of two consecutive injections of amobarbital, ipsilateral and contralateral to the epileptic focus. We studied whether a bilateral IAP has added value to a unilateral, ipsilateral IAP.

Methods. This population-based study included 183 consecutive patients referred between 1997 and 2002 for screening for TLE surgery who underwent bilateral IAP. Using multivariable modeling, we assessed the added value of bilateral IAP on the decision for surgery, resection size, amygdalohippocampectomy, postoperative seizure freedom, memory performance, and IQ change.

Results. Given the results from the unilateral IAP, the bilateral IAP had added prognostic value for postoperative change in verbal memory ($p<0.01$) and verbal IQ ($p<0.01$), especially if patients had a left-sided focus. In contrast, information provided by the contralateral IAP was not associated with decision-making or surgical strategy.

Conclusions. We conclude that a bilateral IAP has added value in predicting postoperative verbal memory and IQ. A bilateral IAP is currently not used to guide surgical strategy, but may be used for this purpose when verbal capacity is of particular concern in patients with a left-sided focus. In all other cases, IAP should be performed unilaterally.

Introduction

The intracarotid amobarbital procedure (IAP, Wada test) is part of the presurgical screening for temporal lobe epilepsy (TLE) surgery to assess language lateralization and the risk of developing post-surgical global amnesia. Often, two injections are applied: the first ipsilateral and the second contralateral to the presumed focus side. IAP is an invasive test with a complication rate of up to 1%.[86-88] The true value of the IAP, however, is increasingly under discussion.[89-91] Recently, the added value of the bilateral IAP in predicting memory decline after TLE surgery was debated.[92;93] This prompted us to systematically quantify the added value of the bilateral IAP beyond the unilateral IAP.

In the Netherlands, all patients referred for epilepsy surgery enter the same Dutch Collaborative Epilepsy Surgery Program (DCESP), a nation-wide tertiary referral program in which all patients undergo the same presurgical work-up.[17] After each single test, a multidisciplinary taskforce decides whether the patient will be eligible or ineligible for surgery, if additional tests are needed to make this decision, and what surgical strategy is needed. When a patient is considered eligible for surgery, a bilateral IAP is standardly performed. A minimum residual memory score after ipsilateral injection is an eligibility criterion for TLE surgery.[17;94]

The Dutch setting provided the ideal opportunity to quantify in a large series of patients the true value of the contralateral IAP in the surgical decision-making and in the prediction of postsurgical outcome. In the Dutch program, a minimum residual memory score after ipsilateral injection is an eligibility criterion for TLE surgery.[17;94] Therefore, our study concentrates on the role of the second, contralateral injection. As a bilateral IAP seems to predict memory decline after surgery,[89;91] we hypothesized it results would also be used in the surgical decision-making. Specifically, if the bilateral IAP indicates a high risk of memory decline, we expect a smaller surgical resection size in these patients.

Methods

Patients

This retrospective study included all consecutive patients who were referred to the Dutch Collaborative Epilepsy Surgery Program between July 1997 and July 2002 for diagnostic work-up to determine eligibility for TLE surgery. The present analysis focused on the 183 patients who were considered eligible for surgery (based on previous tests) and subsequently underwent a bilateral IAP. To address the aim to assess the added contribution of the second IAP injection to set the decision for or against surgery, all 183 patients were included. To address the other aims - assessing the added value of the second IAP to decide on the extent of surgery and the added prognostic or predictive value of postoperative outcomes - only the 178 patients who were actually operated were included.

Intracarotid amobarbital procedure

Both IAP injections were performed in the awake patient after transfemoral catheterization of the internal carotid artery, using the Seldinger technique. First, on the side of the expected seizure focus a small amount of radio-opaque contrast was given and a carotid angiogram was performed. The actual test then started and was monitored with EEG and videotaped. In adults, on average 125 mg amobarbital was injected; in children usually 100 mg, depending on weight and age. After 30 minutes, the same procedure was performed on the side contralateral to the expected focus. In case of insufficient amobarbital effect during the first injection, a repeated injection with a higher dose was given after 30 minutes.

After injection resulting in contralateral paresis of the arm, the neuropsychologist assessed language function during 2 to 3 minutes, testing object naming, comprehension of spoken and written tasks, picture description, spontaneous speech, and the Token Test.[95] Language dysfunction was defined by the occurrence of dysnomia, paraphasia or incongruous mistakes on comprehension tasks after injection.[94] Two-and-a-half minutes after the injection five items were presented to the patient to remember. Fifteen minutes after

injection, the patient was asked to recall each of these items by choosing one out of four visually presented alternatives. The delayed memory score consisted of the number of recalled items, each accounting for 20% of the sum score. If a wrong item was recalled, but the category was correctly named spontaneously (e.g. 'it was a card with a stamp'), this was scored as half correct (10%).[94] To undergo ipsilateral TLE surgery, a residual delayed memory score of at least 50% during the ipsilateral injection was required. More details of our IAP protocol can be found elsewhere [94].

Neuropsychological tests

A standard battery of neuropsychological tests was performed within 6 months before surgery, and repeated 6-9 months after surgery.[96] We specifically looked at results from tests of verbal and nonverbal memory. Verbal memory tests included (1) the Fifteen Word Test, a verbal learning test, which is a Dutch adaptation of Rey's Auditory Verbal Learning Test, which scores immediate and delayed recall; (2) the Visual Naming Task, a 15 item test of black-and-white drawings, which scores both number of errors and time to complete; (3) Digit Span Forward as a test of auditory alertness and audioverbal recall. The nonverbal memory test included the Rey-Osterreith Complex Figure Task with scoring of immediate and delayed reproduction. Initial preoperative test performance was expressed qualitatively as normal for verbal and nonverbal memory, or in the lower (lowest quartile of the distribution of the general population) or upper (highest quartile) range. Change in scores postoperatively was also expressed qualitatively as improved, unchanged or deteriorated. Furthermore, we assessed change in verbal IQ and performance IQ assessed with the Dutch version of the Wechsler Adult Intelligence Scale from 1970 (WAIS III),[97] within 6 months before and 2 years after surgery.

Surgery

In the Netherlands, eligible TLE patients usually undergo a tailored temporal lobe resection with amygdalohippocampectomy. In mesiotemporal lobe epilepsy with mesiotemporal sclerosis only, a standard resection with

amygdalohippocampectomy is performed and when appropriate surgery consists of a lesionectomy without amygdalohippocampectomy. Tailoring is done using intraoperative electrocorticography.[96] Selective amygdalohippocampectomy is not performed.

Study outcomes

To assess the contribution of the second IAP injection to the decision-making, the consensus decision by the Dutch multidisciplinary taskforce was taken as outcome. To study the influence of results from the second IAP injection on the extent of surgical resection, outcomes were the size of the lateral temporal resection in centimeters and whether or not the resection included an amygdalohippocampectomy.

The prognostic outcomes after surgery included postoperative seizure freedom, change in memory performance and IQ change. Postoperative seizure freedom was defined as the total absence of seizures (including auras, Engel classification IA) one year after surgery.[98] For memory performance, equal or improved postoperative verbal and nonverbal memory was defined as a positive outcome. Changes in verbal and performance IQ (post- minus preoperative values) were taken as continuous outcome variables.

Data analysis

We quantified in how many patients the positive decision for surgery before the IAP was altered into a decision not to perform surgery and we related this to the memory scores of the ipsilateral and contalateral IAP injection.

To assess the contribution of the contralateral IAP injection to the dichotomous decision for amygdalohippocampectomy we fitted two consecutive logistic regression models, one with only the results of the first ipsilateral IAP injection and one after adding the results of the second IAP injection. Models were fitted both for IAP memory score results and for IAP language lateralization results. The difference between the two models - to determine whether the second

injection had indeed added predictive value - was assessed with the likelihood ratio test. Similarly, for predicting the continuous outcome (surgical resection size), two consecutive linear regression models were fitted. The same analytical approach was used for quantifying the added prognostic value of the second IAP test to determine seizure freedom after surgery and change in memory performance (dichotomous outcome: logistic regression) and to determine change in IQ (continuous outcome: linear regression).

Results

The epileptic focus was left-sided in 104 (57%) out of 183 patients. Table 5.1 shows the patient characteristics. Five patients (3%) did not undergo surgery and 178 (97%) were operated on.

Table 5.1. Patient characteristics (mean ± standard deviation)

Preoperative characteristics		N=183
Sex (% male)		48
Age at onset epilepsy (years)		13 ± 9
Age at surgery (years)		35 ± 11
Focus side (% left)		57
MTS on MRI (%)		47
Other lesion on MRI (%)		27
Verbal memory performance	In lower quartile (%)	38
	Normal (%)	56
	In upper quartile (%)	6
Nonverbal memory performance	In lower quartile (%)	42
	Normal (%)	54
	In upper quartile (%)	4

Table 5.1. Continued

Preoperative characteristics		N=183
Verbal IQ		102 ± 15
Performance IQ		107 ± 15
Memory score during ipsilateral IAP		90 ± 16
Memory score during contralateral IAP		65 ± 31
Language lateralization	Left (%)	87
	Right (%)	6
	Bilateral (%)	7
	Ipsilateral to focus side (%)	49
	Contralateral to focus side (%)	44
Surgical and postoperative characteristics		N=178
Side of surgery (% left)		56
Intraoperative electrocorticography (%)		67
Intraoperative speech mapping (%)		13
Amygdalohippocampectomy performed (%)		94
Resection size (cm)		4.0 ± 1.3
Seizure freedom (% Engel 1A)		65
Seizure freedom (% Engel 1 or 2)		89
Verbal memory performance	Improved (%)	17
	Unchanged (%)	55
	Deteriorated (%)	28
Nonverbal memory performance	Improved (%)	22
	Unchanged (%)	66
	Deteriorated (%)	22
Postoperative verbal IQ		105 ± 15
Postoperative performance IQ		112 ± 14

Value of contralateral injection on surgical decision-making

The memory score on the ipsilateral IAP indicated that five patients (3%) were at risk of global amnesia. Nevertheless, one of these (left-sided focus) was considered eligible for a modified resection, i.e. lesionectomy of an oligodendroglioma without amygdalohippocampectomy. This decision was based on the results of the first IAP only in combination with findings from MRI and video-EEG monitoring. Of the 178 patients with an adequate memory score on the ipsilateral IAP, one patient experienced a spontaneous reduction in seizure frequency and severity and did not want to proceed with surgery. The results of the second IAP again played no role.

Surgery consisted of tailored anterior temporal resection. Given information from the first IAP, information from the second contralateral IAP had no added value on either amygdalohippocampectomy or resection size (table 5.2). This applies to the IAP memory results as well as to IAP language lateralization results.

Prognostic value of contralateral injection

Of the 178 operated patients, 115 (65%) were completely seizure free one year after surgery. Information from the second contralateral IAP had no added value to that from the first injection, in the prediction of seizure freedom one year after surgery (table 5.3). Language ipsilateral to the resection side (information from first injection) was predictive of worse seizure outcome, while bilateral language (information from both injections) seems more predictive of good seizure outcome. The latter, however, was not statistically significant. Furthermore, the predictive value of ipsilateral language function on a worse seizure outcome was fully explained by focus side: left-sided focus was associated with worse seizure outcome: OR=0.41 (95% CI: 0.21-0.79, data not shown).

A combination of a high memory score on ipsilateral and a low score on contralateral injection was associated with better verbal memory outcome after surgery (table 5.4). For language lateralization there was no added predictive value

of the contralateral IAP.

Table 5.2. Predictive value of memory function and language of the two IAP injections on the extent of surgery.

Prediction of extent of surgery	*First injection*		*First and second injection*	
	OR	***95% CI***	***OR***	***95% CI***
Amygdalohippocampectomy (yes/no)				
IAP memory score (per 10%)				
Ipsilateral injection	1.08 [a]	1.04-1.13 **	1.08	1.04-1.13 **
Contralateral injection			0.99	0.97-1.01
IAP language (yes /no)				
Language ipsilateral to focus	0.28	0.06-1.33	0.28	0.06-1.38
Language bilateral			0.83	0.09-7.41
Resection size (cm)	***RC***	***95% CI***	***RC***	***95% CI***
IAP memory score (per 10%)				
Ipsilateral injection	0.003 [b]	-0.01 – 0.02	0.003	-0.01 – 0.02
Contralateral injection			0.002	0.00 – 0.01
IAP language (yes /no)				
Language ipsilateral to focus	-0.549	-0.92 – -0.18 **	-0.564	-0.94 – -0.19 **
Language bilateral			0.164	-0.62 – 0.95

*OR = odds ratio; RC = regression coefficient; 95% CI = 95% confidence interval; ** p-value < 0,01*

[a] this OR means that the odds (probability) of amygdalohippocampectomy is 1.08 times higher for every 10% increase in the memory score on ipsilateral IAP.

[b] this RC represents the slope of the plot between the resection size in cm and memory score on ipsilateral IAP per 10%, i.e. with a RC of 0.003 the regression line is almost horizontal, indicating no clinically relevant association between resection size and memory score.

Table 5.3. Predictive value of memory function and language of the two IAP injections on seizure freedom.

Prediction of seizure freedom (yes / no)	*First injection*		*First and second injection*	
	OR	***95% CI***	***OR***	***95% CI***
IAP memory score (per 10%)				
Ipsilateral injection	1.02	1.00-1.04	1.02	1.00-1.04
Contralateral injection			0.99	0.98-1.01
IAP language (yes / no)				
Language ipsilateral to focus	0.49	0.26-0.93 *	0.45	0.23-0.85 *
Language bilateral			3.54	0.72-17.33 [a]

*OR = odds ratio; 95% CI = 95% confidence interval; * p-value < 0.05*

[a] *the wide 95% CI is because only 13 patients had bilateral language lateralization.*

In general, verbal and performance IQ increased after surgery (table 5.1, p-value<0.01 for both). A bilateral IAP showing language contralateral to the focus side or bilateral language was predictive of a postoperative increase in verbal IQ, although information from the first IAP injection only conferred no prognostic information for IQ change (table 5.5).

Table 5.4 Predictive value of memory function and language of the two IAP injections on the post-operative verbal and nonverbal memory change.

Prediction of memory change	*First injection*		*First and second injection*	
	OR	*95% CI*	*OR*	*95% CI*
Verbal memory				
IAP memory score (per 10%)				
Ipsilateral injection	1.02	1.00-1.05 *	1.02	1.00-1.05 *
Contralateral injection			0.98	0.97-0.99 **
IAP language (yes / no)				
Language ipsilateral to focus	0.14	0.06-0.30 **	0.12	0.06-0.27 **
Language bilateral			4.69	0.95-23.22
Nonverbal memory				
IAP memory score (per 10%)				
Ipsilateral injection	1.04	1.02-1.07 **	1.04	1.02-1.07 **
Contralateral injection			0.99	0.98-1.00
IAP language				
Language ipsilateral to focus	0.34	0.14-0.82 *	0.35	0.15-0.85 *
Language bilateral			0.76	0.18-3.12

*OR = odds ratio; 95% CI = 95% confidence interval; * p-value < 0.05; ** p-value < 0.01*

Table 5.5. Predictive value of memory function and language of the two IAP injections on the post-operative change in verbal and performance IQ.

Prediction of IQ change	*First injection*		*First and second injection*	
	RC	*95% CI*	*RC*	*95% CI*
Verbal IQ				
IAP memory score (per 10%)				
Ipsilateral injection	0.064	-0.02 – 0.15	0.062	-0.02 – 0.15
Contralateral injection			-0.037	-0.08 – 0.00
IAP language (yes / no)				
Language ipsilateral to focus	-1.884	-4.31 – 0.54	-2.611	-5.02 – -0.20 *
Language bilateral			7.908	2.92 – 12.90 *
Performance IQ				
IAP memory score (per 10%)				
Ipsilateral injection	0.057	-0.05 – 0.16	0.058	-0.05 – 0.16
Contralateral injection			0.018	-0.03 – 0.07
IAP language (yes / no)				
Language ipsilateral to focus	1.559	-1.34 – 4.56	1.367	-1.59 – 4.32
Language bilateral			2.091	-4.03 – 8.21

*RC = regression coefficient; 95% CI = 95% confidence interval; * p-value < 0.05*

Subgroup analyses

To assess whether the above findings were different across specific patient characteristics, the analyses were repeated for four subgroups: mesiotemporal sclerosis on the MRI (N=85); a lesion on the MRI (N=48); a left-sided and a right-sided epileptic focus (N=100 and N=78, respectively). No different results were found. The presence of a left-sided epileptic focus fully explained the added value of the memory score of the contralateral IAP on change in verbal memory: OR=0.98

(95% CI: 0.97-0.99), while no added value was found in the subgroup with a right-sided focus.

Discussion

Clinical findings

This study assessed the true or added value of the bilateral IAP in the presurgical evaluation of TLE, as compared to the unilateral IAP. More specific, we looked whether the prognostic value of the bilateral IAP for memory performance after surgery, was actually reflected in the extent of the surgical resection. The contralateral IAP showed added prognostic value for both postoperative verbal memory (using information from memory scores) and verbal IQ (from language representation), especially in left-sided cases. However, we did not find any influence or added value of the contralateral IAP on the decision to operate, nor on the extent of the surgical resection. This indicates that in the Netherlands, contralateral IAP information is currently not used in clinical decision-making.

An explanation for the lack of incorporation of contralateral IAP results in surgery strategy may be that the neurosurgeons in the Netherlands rely on electrocorticographical tailoring of the resection, regardless of IAP results. Also, the clinical relevance of a decline in postoperative memory on neuropsychological tests is not clear, as it may not reflect the patient's experience. Thus, a patient with a significant decline in verbal memory after surgery, may nevertheless report an overall improvement in quality of life.[99]

The use and value of IAP in TLE surgery, is increasingly under debate.[89-91] Two recent studies showed that IAP, either unilateral or bilateral, is not essential to predict memory decline after surgery when the results of other, noninvasive diagnostic tests are taken into account.[92;93] We were not able to test the clinical value of the ipsilateral injection - which is commonly used to assess the safety of a planned hippocampal resection (memory) and tailored neocortical resection (language).[16;100;101] We rather focused on the added value of a bilateral compared to a unilateral IAP. Two other studies also evaluated the independent prognostic

value of the contralateral IAP injection on postoperative verbal memory performance after TLE surgery. Sabsevitz et al. assessed both the ipsilateral and contralateral IAP and Stroup et al assessed the contralateral IAP.[102;103] Our results are in line with both studies, i.e. results from the contralateral IAP were predictive of postoperative verbal memory decline. Most IAP studies used memory asymmetry scores to predict seizure freedom and memory outcome after surgery.[94;104-106] The prognostic value of asymmetry scores (ipsilateral minus contralateral memory score) was confirmed by our data for change in verbal and nonverbal memory performance (both OR 1.02; 95% CI 1.01-1.03) and for change in performance IQ (RC 4.79; 95% CI 3.00-6.58). Interestingly, and, as far as we know no-one explored this earlier, a consequent influence on surgical strategy was not confirmed by our data. This shows that the true value of a test may not be valued by the very clinicians who use it.

In patients who fail the IAP, Lacruz et al. showed that in case of a low memory score after ipsilateral injection, selective amygdalohippocampectomy has a more favorable outcome than standard temporal lobectomy.[107] In the Dutch program, selective amygdalohippocampectomy is not performed. We did find that patients with a higher residual memory score on ipsilateral injection were more likely to undergo (additional) amygdalohippocampectomy. As expected, in patients with language ipsilateral to the focus side, resections ended up smaller (mean resection size of 3.8 cm compared to 4.3 cm; p-value <0.01). Nevertheless, no added value of the contralateral IAP was found.

Methodological issues

Some methodological issues merit consideration. IAP protocols notoriously differ between centers, especially with regard to timing of presentation, modes and number of memory items. Such a lack of standardization somewhat limits the extensibility of our results and may explain discrepancies with other studies. Interpretation of IAP results may also differ. Our IAP protocol used the memory score after ipsilateral injection as eligibility criterion for TLE surgery.[94] In the Dutch

program, the IAP is considered a test of functional memory reserve of the hemisphere contralateral to the side of injection.[101;108;109] In other centers it is asymmetry in memory scores after ipsilateral and contralateral injections that is used as pass/fail criterion.[94;107]

Second, in our protocol the two IAP injections were performed 30 minutes apart. Other centers use longer periods in between the two injections, or even perform them on different days.[110] Performing a second injection on the same day implicates a risk of misclassification of the memory score after the second injection.[110;111] Performing the second injection on another day, however, is inconvenient to the patient and probably increases the risk of morbidity.[112] An increasing number of international centers now perform IAP unilaterally.[113]

Third, the decision whether or not to perform surgery was a consensus decision by the national Dutch taskforce. Since a formal reference standard to determine (in)eligibility for TLE surgery is lacking, such a consensus decision is generally considered the best alternative.[2;3;8;9] Nevertheless, we do not know how many patients were actually inappropriately operated or rejected for surgery. We believe the decision for surgery of the Dutch taskforce was adequate, since the seizure outcome in our operated patients is comparable to that reported in the literature, 65% of all patients being seizure free without auras (Engel class 1A) one year after TLE surgery.[13;14]

Finally, the neuropsychologists involved in postoperative tests were not blinded to the results of the IAP, which might have introduced bias in interpreting the results.[8] Also, a learning curve between preoperative and postoperative tests could have influenced the results. The influence of learning curve effects on the results is minimized by e.g. the use of different sets of word lists in the repeat test. Also, the event of surgery between the tests will mitigate the learning curve effect.

Conclusion

We confirm that in the prediction of postoperative verbal memory decline and verbal IQ change, the contralateral IAP injection has added value, especially in left-

sided TLE surgery. Nevertheless, we found no evidence that information from the contralateral IAP is currently used in surgical decision-making. We propose that a bilateral IAP should be reserved for patients with a left-sided focus for whom verbal memory and IQ are especially critical, e.g. to professional performance. In other cases, our data do not support the routine use of a bilateral IAP. Refraining from a contralateral injection in these cases would improve the safety and cost-effectiveness of TLE surgery.