Technologies used to visualise the seizure focus in people with refractory epilepsy

The clinical effectiveness and cost-effectiveness of technologies used to visualise the seizure focus in people with refractory epilepsy being considered for surgery: a systematic review and decision-analytical model

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Executive summary

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Executive summary

Background

Up to 20–30% of patients with epilepsy continue to have seizures despite ongoing treatment with one or more antiepileptic drugs; most have symptomatic or cryptogenic localisation-related epilepsy. For these patients, surgical resection of the epileptic focus may be considered, and can result in seizure freedom. The initial stage of the work-up for epilepsy surgery to isolate the seizure focus and identify the underlying aetiology is the conduct of surface electroencephalography (EEG) and routine magnetic resonance imaging (MRI); further non-invasive tests and invasive/intracranial EEG (iEEG) may be undertaken. Currently, non-invasive tests provide information to inform the scope and positioning of iEEG electrodes. However, non-invasive technologies may be able to replace iEEG, in at least some patients, if their accuracy allows location of a seizure focus to be established. There is a range of non-invasive technologies available, including single-photon emission computed tomography (SPECT), subtraction ictal SPECT coregistered with MRI (SISCOM), positron emission tomography (PET), magnetoencephalography (MEG) and specialist MRI technologies. A previous, broad-ranging, health technology assessment (HTA) published in 2006 identified several limitations associated with the available clinical evidence in this therapeutic area, primarily the lack of studies of effectiveness. In order to inform clinical practice, studies need to investigate the clinical value of a test, and the impact of the results of that test on the decision-making process and subsequently on clinical outcomes.

Objectives

This review aimed to evaluate the diagnostic accuracy, clinical utility and cost-effectiveness of non-invasive technologies over and above routine EEG/MRI, and whether any further diagnostic procedures should be undertaken in individuals for whom there is a reasonable hypothesis for the site of the seizure focus, but in whom that focus has not been reliably identified after the initial surface EEG and MRI. The review addressed five research questions: the diagnostic accuracy of the non-invasive technologies of interest, and the limitations of these studies; the association of non-invasive test results with a good outcome following surgery; the impact of non-invasive technologies on the decision-making process; which diagnostic strategy is the most cost-effective option for patients with refractory epilepsy who are undergoing presurgical work-up; and what the gaps are in the current evidence base, and how these can be addressed. A decision-analytical approach is presented, which provides a potential framework for combining this information with additional resource use and value parameters that are also required to inform decisions concerning the cost-effectiveness of tests.

Methods

A systematic review was conducted to evaluate the clinical effectiveness, diagnostic accuracy and cost-effectiveness of high-density electroencephalography (HD-EEG), specialist MR technologies, SPECT, PET, MEG, SISCOM or magnetic source imaging (MSI) in patients with refractory partial epilepsy not caused by tumours, vascular malformations or trauma being

considered for surgery, where the decision to go to surgery and/or the outcome following surgery was reported. Eighteen electronic databases were searched without language restrictions from 2003 to July 2010 [including MEDLINE, EMBASE, BIOSIS Previews, PASCAL, ClinicalTrials.gov, and The Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL) and the Cochrane Register of Diagnostic Studies]; studies prior to 2003 were identified from a prior HTA review. Reference lists of included studies and relevant reviews were also searched, and a citation search of key papers undertaken. We sought single-gate (cohort) diagnostic accuracy studies that reported the final diagnosis/decision to undertake surgery and/or the outcome following surgery in those who underwent an excisional procedure; studies that undertook a multivariate regression analysis in which an index test(s) of interest was an independent variable; cohort studies and randomised controlled trials (RCTs) comparing two or more diagnostic tests of interest that reported the number in each arm that progressed to surgery and/or post-surgical outcome; and studies that reported the impact of test(s) on the decision to go to surgery and the outcome following surgery; and cost-effectiveness studies of alternative technologies used to visualise seizure focus in people with refractory epilepsy being considered for surgery. Study selection was conducted by two independent reviewers using pre-specified inclusion criteria. Study quality was assessed using an adapted Quality Assessment of Diagnostic Accuracy Studies (QUADAS), with additional criteria relating more generally to observational studies.

No RCTs were identified that met the inclusion criteria. Data from the diagnostic accuracy studies were extracted into 2×4 contingency tables and rates of correctly localised (hits), non-localised (misses) and wrongly localised (errors) tests, and likelihood ratios were also calculated. From outcome prediction studies the measure of association and the level of significance was extracted for index tests included in a multivariate regression analysis. From the studies reporting the impact of an index test on the decision-making process, the number of patients for whom the decision relating to surgery changed or not were extracted. Studies were combined in a narrative synthesis.

A decision-analytical model was developed to evaluate the incremental cost-effectiveness of alternative imaging strategies in people with medically refractory epilepsy who are being considered for surgery, and that have already undergone a video-EEG and MRI which has resulted in an indeterminate result (i.e. the decision to proceed to surgery is uncertain), based on the only decision study included in the review of clinical effectiveness. The model therefore provides an illustration of how data from appropriately designed clinical studies can be used to inform a decision model to evaluate the cost-effectiveness of imaging technologies in the presurgical evaluation of epilepsy surgery.

The model comprises a short-term element characterising the period over which these imaging strategies are applied and a management strategy employed and a long-term element, which considers the costs and outcomes over the remaining lifetime of the patient. A lifetime time horizon is used and costs are evaluated from the perspective of the NHS and Personal Social Services, expressed in UK pounds sterling at a 2010 price base. Outcomes in the model are also expressed in terms of quality-adjusted life-years (QALYs). Both costs and outcomes are discounted using a 3.5% annual discount rate as is consistent with current National Institute for Health and Clinical Excellence guidelines (2008). An analysis of the impact of uncertainty was also undertaken, focusing on the impact of uncertainty over each of the model's input parameters and an analysis of the impact of alternative structural assumptions.

Results

Clinical effectiveness results

The searches identified 3251 citations; 534 were retrieved for full paper screening, of which 161 were abstracts. Eighteen studies met the inclusion criteria ($n = 1312$; range 24–469). None was a RCT or cohort study comparing outcomes between patients who received different combinations of imaging techniques that reported the decision to go to surgery and/or outcome following surgery. Thirteen were single-gate diagnostic accuracy studies, seven were outcome prediction studies and one was a decision study. Overall, the study quality was poor.

Classification of the test results from the diagnostic accuracy studies in order to determine their contribution to the decision-making process was not possible. The number of index tests that were correctly localising as indicated by a good surgical outcome ranged from 6% to 96%, depending on the index test and the definition used to define a good surgical outcome; the proportion of tests that could not be classified as a hit, miss or error was high – up to 53%. The likelihood ratios, both for the decision to go to surgery and outcome following surgery were close to unity and inconsistent across studies.

The outcome prediction studies that reported sufficient individual patient data in order to conduct binary logistic regression analyses were very heterogeneous. Limitations in the data available and sample sizes precluded any conclusions being drawn from these studies regarding the predictive ability of the tests evaluated.

One study reported the impact of imaging fluorodeoxyglucose positron emission tomography (FDG-PET) on the decision-making process. Of the 110 patients who received FDG-PET, the decision for or against surgery was considered to be influenced by the results of the FDG-PET scan in 78 patients (71%): 48 influenced the decision in favour of surgery; 28 in favour of no surgery; and two patients had doubt cast on prior decisions and eligibility for surgery became uncertain. The positive decision predictive value for PET was 65% [95% confidence interval (CI) 53% to 77%] and negative decision predictive value was 60% (95% CI 45% to 72%). As this was the only study to meet the inclusion criteria that provided evidence on the decision-making process or clinical effectiveness of any of the index tests, it was used in the development of the decision-analytical model. Three strategies were considered in the model:

1. All patients with indeterminate results from MRI/EEG receive medical management (MM).
2. FDG-PET is performed – if the result does not lead to a positive or negative decision to undertake surgery then the patient receives MM.
3. FDG-PET is performed – if the result does not lead to a positive or negative decision to undertake surgery then iEEG is offered; the result of this test determines the management strategy (S+, proceed to surgery; S– and S?, MM).

The decision-analytical model suggested that Strategy 3 appeared to be the most cost-effective, at conventional cost-effectiveness thresholds of £20,000–30,000. When the additional benefits conferred over the longer term on patients who received surgery compared with MM alone [i.e. the benefits over and above those attributed to the additional success rate of surgery in increasing the probability of patients becoming seizure free (SF) at 1 year] were excluded, MM appeared the more appropriate management strategy for patient in whom the decision to proceed to surgery was still unclear following the results of FDG-PET.

Discussion

The main finding of the review of clinical effectiveness is that the available evidence is inadequate to reliably inform clinical practice. There is a lack of studies evaluating the impact of these tests on clinical decision-making and patient outcomes; only one such study met the inclusion criteria. A framework was developed to inform evaluations of the cost-effectiveness of alternative imaging strategies in people with medically refractory epilepsy who are being considered for surgery based on the one decision study identified in the clinical review, therefore it was not possible to assess the full range of potential strategies required to inform NHS practice. The findings need to be considered in light of the limited clinical data identified, and the assumptions required to link these data to long-term costs and outcomes that are suitable for informing cost-effectiveness analysis.

These initial results are important for several reasons. First, they provide an indication that non-invasive testing (at least with FDG-PET) appears cost-effective. Second, it is feasible to assess cost-effectiveness based on appropriately designed clinical effectiveness studies. Third, the model structure provides both a framework and set of inputs/results that could be revised and updated as new evidence emerges. The model could be adapted to evaluate additional alternative diagnostic strategies (i.e. expanding the existing tree 'vertically') or additional subsequent tests following a non-definite decision to undertake surgery (i.e. strategies may be more complex, involving a larger number of tests used sequentially); which adaptation is chosen will impact on the type of data required. Finally, the model demonstrates that the value of the diagnostic strategies is inextricably linked both to their impact on the decision to proceed to surgery or not and to the cost-effectiveness of the subsequent treatments.

Future studies need to investigate the impact of the test results on the decision-making process and subsequent clinical outcomes; single-gate diagnostic accuracy studies are not useful in this capacity. RCTs could be beneficial; however, their conduct in this indication may be considered impracticable for a number of reasons, including ethical issues. A single RCT has been performed in this area (unfortunately its population was not relevant for our review), demonstrating the feasibility of such trials. Observational studies in which all patients are given subjected to both diagnostic technologies can generate informative data as long as the necessary information is gathered and patients are selected based on their clinical problem, so representing clinical practice. As well as data on the influence of test results on consensus diagnosis and resultant management decision, clinical outcomes in patients who do not undergo surgery, compliance with tests and surgery, quality of life and complication and re-operation rates are important.

The feasibility of developing a national registry to collect standardised information regarding the diagnostic pathway should be considered. Such a database would allow trends in clinical practice to be observed, identification of interventions and populations that would benefit from further investigation, and data for future decision-analytical modelling. Decision modelling will be an important analytical method, synthesising data from a range of sources and simulation of the impact of various diagnostic strategies including which combinations of tests is optimal on patient outcomes. Evidentiary assumptions about test performance and clinician decision-making can be investigated, as can an examination of benefits, harms and costs together to provide cost-effectiveness and cost–utility information to decision-makers.

Future research needs to be considered in relation to how the research informs the different levels of the diagnostic evaluation framework, and ultimately how this links to the decision problem(s) faced by clinicians and the NHS. It is integral to the evaluation of diagnostic technologies in the work-up for epilepsy surgery that their impact on clinical decision-making, and on further

treatment decisions, is considered; findings from these studies should be used alongside assessments of the long-term clinical effects and of costs of such treatments. The role of decision modelling is central to this, ultimately helping the NHS to make informed decisions over the appropriate use of imaging technologies in this context.

Conclusions

Clinical research into imaging for the localisation of epileptic foci is abundant but not adequately informative because:

- There is no acceptable reference standard for the assessment of the diagnostic accuracy of tests to identify a seizure focus in patients with refractory epilepsy.
- Diagnostic accuracy studies reporting clinical outcomes tend to do so only following surgery.
- The outcome prediction studies identified are based only on patients who have undergone surgery, and have small sample sizes.
- Decision level and effectiveness studies are lacking.

The additional value of any diagnostic strategy for the localisation of epileptic foci is closely related to the impact on treatment decisions as well as the value of the treatments themselves (MM or surgery); this needs to be considered fully in informing cost-effectiveness assessments in this context. Therefore, future appropriately designed studies need to determine the added value of diagnostic regimens in terms of informing decisions on the appropriateness of surgery and in terms of clinical effectiveness and cost-effectiveness. The feasibility of developing a national registry should be considered to collect standardised information regarding the diagnostic pathway, decisions made along the pathway, and clinical outcomes, for all patients who receive work-up to determine whether or not they are eligible for epilepsy surgery. Existing and future research needs to be considered closely in relation to how the research informs the different levels of the diagnostic evaluation framework and ultimately how this links to the actual decision problem(s) faced by clinicians and the NHS; the role of decision modelling is central to this more general issue.

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Publication

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