Outcomes in clinical trials evaluating interventions for the prevention and treatment of hepatic encephalopathy

Short title: Trial endpoints in hepatic encephalopathy

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Randomised clinical trials and systematic reviews of research findings can provide high-quality evidence for decision-making in the management of patients with hepatic encephalopathy. A large number of clinical trials have been undertaken, over the last 50 years, for the prevention and treatment of this condition. However, changes have been made, during this time, in the classification of hepatic encephalopathy, diagnostic criteria, and assessment measures. These temporally–based changes and the consequent lack of standardisation make it difficult to compare interventions and to evaluate their comparative efficacy and safety. While some consensus has been reached in relation to the diagnostic evaluation, classification and monitoring of patients in clinical trials there is less surety about the choice of clinical endpoints. These outcome measures should be universally applicable, easily measured and clinically relevant. This paper reviews the current recommendations regarding outcome selection and outlines some of the potential problems and pitfalls inherent in clinical trials evaluating interventions for the management of hepatic encephalopathy.

Hepatic encephalopathy is the term used to describe the spectrum of neuropsychiatric change that can occur in people with liver insufficiency and/or portal systemic shunting.[1] Clinically apparent or *overt* hepatic encephalopathy manifests as a variety of mental and motor disorders.[2] It may develop spontaneously over a period of hours or days although, in the majority of patients, an obvious precipitating factor such as: treatment non-compliance, dehydration, constipation, infection or gastrointestinal bleeding, is identified.[3] Episodes may recur; less frequently the neuropsychiatric abnormalities persist.[2] *Minimal* hepatic encephalopathy is the term used to describe the neuropsychiatric status of people with liver disease who appear clinically normal but show abnormalities in neuropsychometric /neurophysiological performance.[2]

Hepatic encephalopathy is a common and debilitating complication of cirrhosis. Between 10% to 14% of people with cirrhosis have overt hepatic encephalopathy when they are first diagnosed with liver disease.[4] In people with decompensated cirrhosis, the prevalence of overt hepatic encephalopathy at presentation is around 20 to 30%.[5-8] In people with cirrhosis who have no evidence of neuropsychiatric impairment the risk of developing an episode of overt hepatic encephalopathy, within five years of presentation, varies from 5% to 25%, depending on the presence or absence of other risk factors; the cumulated incidence of overt hepatic encephalopathy is as high as 40%.[9,10] The prevalence of minimal hepatic encephalopathy is likely to exceed 50% in people with previous overt hepatic encephalopathy.[11-13]

The presence of hepatic encephalopathy, whether minimal or overt, is associated with significant impairment in the performance of complex tasks, such as driving,[14,15] and detrimental effects on quality of life,[16] and safety.[17] In addition, the presence of overt hepatic encephalopathy in people awaiting liver transplantation, has a detrimental effect on

neurocognitive function post-transplantation,[18] and on survival.[19-22] The one-year survival rate in people who have hepatic encephalopathy at presentation is 36%, with a five-year survival rate of 15%, [22] while the survival probability after a first episode of hepatic encephalopathy is 42% at one year falling to 23% at three years.[19] Overt hepatic encephalopathy also poses a substantial burden for the carers of affected people[23] and a significant financial burden on healthcare systems.[24,25]

Given the hepatic encephalopathy is such a common and debilitating complication of hepatic encephalopathy the identification of effective and safe interventions for its management is essential.

Evidence –based Approach to the Conduct of Randomised Clinical Trials

The emphasis on evidence-based practice in health-care has stimulated the undertaking of randomised clinical trials evaluating health-care interventions.[26-28] The results from these trials may have a considerable influence on clinical practice and determine the interventions offered to patients. Guidelines exist to ensure that the conduct of randomised clinical trials is optimised focusing on research design and the procedures associated with internal validity and reporting.[29,30] Meta-epidemiological studies have identified a number of design features associated with exaggerated estimates of the effects of interventions, including inadequate/unclear sequence generation and allocation concealment; bias is greatest in trials with subjective rather than objective outcomes.[31,32]

Reviews of randomised clinical trials evaluating interventions in patients with cirrhosis have identified a number of potential methodological problems.[33-35] These include potential biases associated with the allocation of intervention and blinding as well as the extent to which trials allowed generalization of results. However, to date, much less attention has been paid to the

importance of the selection, definition and reporting of trial endpoints; these are key determinants of the quality of the trial and hence the validity of the inferences that can be drawn from the outcomes. The lack of standardised and validated common outcome measures, that are meaningful for patients and health-care professionals, is an important obstacle in assessing interventions; determining their external validity; and, facilitating inter-intervention comparisons.

Trial endpoints for interventions in hepatic encephalopathy

One of the most important considerations in designing any clinical trial is the choice of outcome measures.[36] The selection of the 'primary endpoints' has a considerable effect on the reliability of any trials designed to evaluate the benefit-to-risk profile of interventions.[36] Primary endpoints should be clinically meaningful measures of how patients feel, function and survive.[36] They should be readily measurable and interpretable and should be sensitive to the effects of the intervention. Above all, they should evaluate those measures which are of greatest significant and relevant to the patient's condition and its treatment

The selection of endpoints in trials for the prevention and treatment of hepatic encephalopathy is difficult not least because the pathophysiology of hepatic encephalopathy is complex and remains poorly understood.[37,38] Further, patients with cirrhosis exhibit a spectrum of neuropsychiatric change and this may be reflected in the relative importance of trial endpoints e.g., changes in mental status are of prime importance in trials involving patients with overt hepatic encephalopathy but are generally not as relevant in patients with minimal hepatic encephalopathy, who are, by definition, clinically unimpaired. Patients with cirrhosis also exhibit considerable phenotypic heterogeneity relative to the aetiology and severity of their liver disease, and often have multiple comorbidities; these factors may

independently affect outcomes and so must be factored into the trial design and controls exercised accordingly.

At present, the variables which provide the best primary endpoints, in trials assessing interventions in hepatic encephalopathy, are: mortality, hepatic encephalopathy, serious adverse events, such as hospitalisations for the complications of cirrhosis, and health-related quality of life.

Many outcome measures used in clinical trial do not qualify as 'clinically meaningful endpoints', but are included in randomized clinical trials as surrogate endpoints. Ideally, these surrogates should predict achievement of important effects on clinically meaningful endpoints. However, this is often not the case. Nevertheless, surrogate endpoints are commonly used as they allow performance of randomized clinical trials that are generally smaller in size, shorter in duration and tend to cost less. However, they provide more limited information on efficacy and less reliable assurances about safety given that they are based on smaller safety datasets. Clinicians should be cautious when interpreting the results of trials which employ surrogate endpoints as primary outcome measures, particularly when determining whether interventions should be used in clinical practice.

Currently there are no accepted, validated surrogate endpoints that can be translated into clinically useful outcomes in trials of interventions in hepatic encephalopathy. However, as there is no gold standard for the diagnosis of hepatic encephalopathy, trials, in this field, tend to employ composite endpoints e.g., an assessment of mental status together with a measure of psychometric performance. However, the interpretability of composite endpoints is greatly influenced by the relative weighting of the included components, and this is often ignored.

1. Mortality

Mortality should be routinely documented, in randomised clinical trials, as an efficacy and/or safety outcome.[10,39] It is an objective outcome and is, therefore, free of variability. Previous meta-epidemiological studies have found that mortality is less susceptible to bias in comparison with other outcomes.[31, 32] In addition, mortality has high internal validity as survival is significantly associated with the presence of hepatic encephalopathy.[19-21] Thus, it is likely that interventions which ameliorate hepatic encephalopathy would also influence survival.

Patients with cirrhosis may die as a result of a complication of their liver disease; as a result of pre-existing co-morbidities; or as a result of an incidental event. These deaths are encompassed in an assessment of 'all-cause mortality' which can be ascertained without the need for adjudication. The relative importance of this end-point for assessing the efficacy and safety of interventions varies depending on the severity of the hepatic encephalopathy and the duration of follow-up. Thus, all-cause mortality is an important end-point in the evaluation of interventions in patients with acute overt hepatic encephalopathy where the risk of death is high. However, in many of these trials the follow-up period equates to the treatment period, which tends to be short; hence an effect on mortality could be overlooked and hence underestimated. All-cause mortality is also an important end-point in the assessment of interventional in patients with chronic hepatic encephalopathy where the period of follow-up tends to be more prolonged. All-cause mortality is not, however, a sensitive outcome measure in trials evaluating interventions in minimal hepatic encephalopathy or for the prevention of hepatic encephalopathy. The use of insensitive endpoints might preclude a fair assessment of the effectiveness of an intervention or possibly result in the prolongation of trials of ineffective interventions.

Additional information, of clinical, scientific and regulatory importance, may be obtained by examining disease-specific mortality; unlike all-cause mortality the ascription of liver-related mortality may need adjudication. The primary cause of death should be defined as the underlying disease (or injury), which initiated the train of events resulting in death; in the case of certain complications of cirrhosis, such as, variceal haemorrhage, spontaneous bacterial peritonitis, hepatorenal syndrome and hepatic encephalopathy, the primary cause of death is clearly liver-related. However, in some instances, it may be very difficult to ascribe a primary cause; for example, when death results from aspiration pneumonia developing as a complication of a variceal bleed.

2. Hepatic Encephalopathy

There is no gold standard test for the diagnosis of this syndrome. Rather there are a number of individual techniques, which access different aspects of cerebral function, that can be used either singly, or in combination, as surrogate endpoints. In practice, any measure with a proven relationship with the behavioural, prognostic and, possibly, pathophysiological features of this syndrome can be used as such.[10, 40, 41]

The key requisites for any test or test system are that: (i) they have been validated for use in this patient population; (ii) appropriate normative data are available; and, (iii) controls can be exercised for any associated co-morbidities. As the condition affects several components of cognitive functioning, not necessarily all to the same degree, use of more than one assessment technique is advised. (Table 1) The available guidelines for testing are only loosely proscriptive but do distinguish between testing in clinical and research settings.[1,10] In practice, the selection of assessment tools will be determined largely by factors such as: simplicity of use; accessibility; and cost.

In trials of interventions in patients with *overt* hepatic encephalopathy mental status is often evaluated using the West Haven Criteria,[42] while levels of consciousness are assessed using the Glasgow Coma Score.[44](Table 2 & 3) The detection of the lower grades of change in mental status is often difficult and its inter-observer reproducibility is relatively poor. Thus, it might be advisable to restrict trial participation to those patients with Grade II change or above. The assessment of mental status, given its subjectivity, is not considered sufficiently robust to provide a primary endpoint for interventional trials in these patients. Thus, it is recommended that at least two additional and validated tests are included. (Table 1) Patients with minimal hepatic encephalopathy do not, by definition, exhibit clinically detectable neuropsychiatric change so interventional trials, in this patient population, rely even more heavily on the use of surrogate endpoints which need to robust and rigorously applied. (Table 1)

In view of the difficulties perceived in detecting Grade 1 hepatic encephalopathy it has been suggested that patients with minimal and Grade I change should be combined into a single group --'covert 'hepatic encephalopathy.[1,10] However, it is unclear how informative or valuable this approach would be in assessing the efficacy and safety of interventional trials. Indeed, it has been shown that patients classified as such behave, when tested, as two relatively independent groups.[45, 46]

Surrogate endpoints for hepatic encephalopathy

A number of surrogate endpoints are available.

Psychometric tests

Patients with hepatic encephalopathy show a range of neuropsychometric abnormalities. In consequence, a large number of psychometric tests have been evaluated in this patient

population but none is specific for the diagnosis of this condition. For this reason test batteries are generally more reliable than single tests, and tend to be more strongly correlated with functional status. Of these test batteries the best known and most extensively validated is the Psychometric Hepatic Encephalopathy Score (PHES),[47,48] which comprises of five paper and pencil tests. The PHES test battery is currently recommended as the 'best clinical standard' for the assessment of psychometric status.[1] Test scores need to be normalized for a number of confounding variables; normative data are available in several countries. Computer-based psychometric tests may allow a more precise quantification of reaction times and more refined testing but require further validation.[49]

Critical Flicker Fusion Frequency

Critical Flicker Fusion Frequency (CFF) is a test based on the perception of light as flickering or fused as its frequency changes.[50] It assesses visual discrimination ability and general arousal. Results have diagnostic and predictive validity.[51-53] There are some differential effects in relation to age and the aetiology of the underlying liver disease.[50] Testing requires intact binocular vision and, for some commercial equipment, normal colour vision.

Inhibitory Control Test

The Inhibitory Control Test (ICT) is a computerized, chronometric test of attention and response inhibition. It can be freely downloaded from www.hecme.tv. Patients are shown a series of random letters and are asked to respond to pre-defined sequences designated as targets or lures. Low target and high lure responses indicate poor performance.[54]. The test has greater diagnostic utility if the number of lures (inhibitory ability) is adjusted by the target accuracy (attention ability).[55]. Results have diagnostic and predictive validity.[55] The test data need to be adjusted for age and education and there is a learning effect. The test is

considered difficult to perform by both healthy subjects and patients with cirrhosis, which potentially limits its usefulness.[56]

Stroop test

The Stroop test is based on differences in recognition reaction times to colour stimuli depending on how they are presented. The test evaluates psychomotor speed and cognitive flexibility. Performance on the Stoops test is affected by a number of confounders including: age, sex, and education; population normative data are available in the United States.[57] A smartphone application (EncephalApp_Stroop; www.encephalapp.com) is available

Scan test

The Scan package, or Sternberg test, is a computerized test system based on a digit recognition memory task. It assesses cognitive attention, psychomotor speed and working memory at three levels of increasing difficulty. Scan software provides a *Z* score based on reaction times and errors, corrected for age and education; there is likely to be a leaning effect. There is relatively little information on the diagnostic and predictive validity of the Scan package but some promising early results.[58]

Electroencephalogram

The electroencephalogram (EEG) reflects cortical neuronal activity. The recording procedure does not require patient co-operation and is not subject to learning effects—problems which beset other assessment methods.[59] The main EEG characteristic of this condition is progressive slowing of the mean frequency but this is not specific as similar changes are observed in other metabolic and drug-induced encephalopathies.[60] In interventional trials in hepatic encephalopathy spectral analysis of the recordings is likely to be more informative.[61] Further advances in EEG technology are likely to provide even better quantifiable and more

informative data. The advent of low-cost, wireless headsets might encourage more widespread use of this technique.[62]

Other surrogate endpoints

At present, there are no validated biomarkers that can be used as surrogate endpoints in interventional trials in hepatic encephalopathy. Ammonia plays a key role in the pathogenesis of this syndrome[37, 38] and treatment is generally directed at reducing circulating ammonia levels. However, blood ammonia concentrations do not correlate directly with clinical status or with psychometric/neurophysiological outcomes.[63,64] Nevertheless, blood ammonia concentrations are frequently used as an endpoint in interventional trials in this field; caution must be exercised when interpreting the results.

3. Serious adverse events

Serious adverse events are defined as any untoward medical occurrence that leads to death; is life threatening; requires hospitalisation or prolongation of hospitalisation; or results in persistent or significant disability.[65] Serious adverse events should be one of the primary endpoint in any interventional trial.

4. Health-related quality of life and aspects of daily functioning

The presence of hepatic encephalopathy, whether minimal or overt, has a detrimental effect on patients' health-related quality of life.[16] This variable should be included as a primary outcome variable in some, but not all, intervention trials in hepatic encephalopathy. Thus, its inclusion in the short-term trials undertaken in patients with acute hepatic encephalopathy is unlikely to provide information of value. However, its inclusion in interventional trials in minimal, recurrent and persistent hepatic encephalopathy is likely to be particularly informative.

Health related quality of life can be assessed using a number of generic tools such as, the Sickness Impact Profile[66] and the 36–item short-form (36-SF) questionnaire[67] or the more specific Chronic Liver Disease Questionnaire (CLDQ).[68] These questionnaire have their merits but are not easily applied. In contrast, the European Quality of Life-5 Dimensions (EQ-5D)[69] questionnaire and visual analogue scale, while not disease-specific, are standardized; the EQ-5D is easy to complete, and produces a single index value, which can be compared against country–specific, societal norms.

Patients with hepatic encephalopathy have difficulty performing complex tasks such as driving[14,15] and are prone to injuries because their risk of falls is increased.[17] These factors will impinge on their quality of life and will, to some extent, be captured within this assessment.

Registration and Reporting of Trial Endpoints

Clinical trials should, in line with the policy of the World Health Organisation (WHO) and The International Committee of Medical Journal Editors (ICMJE), be registered in a publically owned, publically accessible registry, and should satisfy a minimum data set.[70, 71] This policy require that any clinical trial initiated after July 1, 2005, irrespective of the assessed intervention, should be prospectively registered as a prerequisite for manuscript submission.[70,71] Trial registration should take place before or at the time of enrolment of the first participant in the trial. This should discourage the changing, omitting, or introduction of endpoints identified after preliminary examination of the clinical trial results.

There are a large number of primary trial registries, most regional based. Collective information from these registries can be accessed *via* two main, publicly available, web-based platforms *viz*, ClinicalTrials.gov, established by the Department of Health and Human Services

through the National Institutes of Health (NIH) and the WHO International Clinical Trials Registry Platform (ICTRP); they provide information on registered trials world-wide.

Although these requirements are well publicised they are frequently contravened. Thus, a review of trial registrations for gastrointestinal interventions in ClinicalTrials.gov, found that many were registered inadequately, often lacking information on basic methodology.[72] Several trials which were subsequently published in journals that subscribed to the ICTRP policy were registered *post hoc*. In others there were discrepancies between the registered trial endpoints and those detailed in the published paper. Likewise, systematic reviews evaluating interventions in patients with cirrhosis have found that several of the included trials were not registered; were registered after the inclusion of the first participant; or reported endpoints which differed from those in the registered protocols. [33-35]

Even journals that strongly support the ICMJE policy on trial registration are not adequately enforcing it. Thus, in a review of trials published in the six highest impact general medicine journals almost a third were registered retrospectively including 10% that were registered after an assessment of the primary endpoints would have been possible.[73]

A lack of consistent registration and reporting of trials is likely to introduce reporting bias which could inflate the estimated benefits of an intervention.[73] More rigorous enforcement of the WHO and ICMJE policy on trial registration is clearly needed.

Conclusion

The conduct and reporting of high-quality randomised clinical trials is essential to ensure evidence-based clinical practice. In the field of hepatic encephalopathy, the assessment of interventions should include clinically relevant primary endpoints such as: mortality, hepatic encephalopathy, serious adverse events and health –related quality of life. In order to ensure

comparison between different interventions, settings and patient populations, these endpoints should be standardised. The lack of a gold standard for the diagnosis of hepatic encephalopathy means that surrogate endpoints need to be employed but none is validated. In consequence the use of composite endpoints is recommended.

CONFLICTS OF INTEREST

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Table 1: Guidelines for the Diagnosis of Hepatic Encephalopathy in Patient with Cirrhosis[1, 10]

Clinical Setting or Single Centre Trial
1. Detailed clinical assessment to identify or exclude clinical change
2. At least two validated tests of which one should be more widely accepted so as to serve as a comparator e.g. PHES
Multicentre-Trial
1. Detailed clinical assessment to identify or exclude clinical change
2. At least two validated tests preferably the PHES plus one test from either of the following two groups: - ICT, Stroop, Scan - EEG or CFF

PHES: Psychometric Hepatic Encephalopathy Score; ICT: Inhibitory Control Test; EEG: Electroencephalogram; CFF Critical Flicker Fusion Frequency

Table 2: West Haven Criteria for Grading Mental Status in Patients with Cirrhosis*

Grade	Features
0	No abnormalities detected
I	Trivial lack of awareness Euphoria or anxiety Shortened attention span Impairment of addition or subtraction
II	Lethargy or apathy Disorientation for time Obvious personality change Inappropriate behaviour
III	Somnolence to semi-stupor Responsive to stimuli Confused Gross disorientation Bizarre behaviour
IV	Coma, unable to test mental state

*Based on the description of the mental state alterations in hepatic encephalopathy originally proposed by Conn et al.[42] as a modification of the Parsons-Smith criteria [43]

Table 3: Glasgow Coma Scale[44] for Grading Level of Consciousness

Variable	Points	Feature
Eye	1	Does not open eyes
	2	Opens eyes in response to painful stimuli
	3	Opens eyes in response to voice
	4	Opens eyes spontaneously
Verbal		Makes no sounds
	1	Incomprehensible sounds
	2	Utters incoherent words
	3	Confused, disoriented
	4	Oriented, converses normally
Motor	1	Makes no movements
	2	Extension to painful stimuli
	3	Abnormal flexion to painful stimuli
	4	Flexion/Withdrawal to painful stimuli
	5	Localizes to painful stimuli
	6	Obeys commands