COMMON REFERENCE-BASED INDIRECT COMPARISON META-ANALYSIS OF INTRAVENOUS VALPROATE VERSUS INTRAVENOUS PHENOBARBITONE IN GENERALIZED CONVULSIVE STATUS EPILEPTICUS

PROTOCOL

Francesco Brigo, Luigi Giuseppe Bongiovanni

Department of Neurological, Neuropsychological, Morphological and Movement Sciences. Section of Clinical Neurology. University of Verona, Italy.

FINAL VERSION

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SECTION 1: INTRODUCTION

Generalized convulsive (tonic–clonic) status epilepticus (GCSE) is the most common and life-threatening form of status epilepticus (SE) (DeLorenzo et al., 1995) with an attributable mortality ranging from 3 to 35% (Cascino et al., 1996). Therefore, it represents a medical and neurologic emergency both in adults (DeLorenzo et al., 1995; Cascino et al., 1996) and in children (Berg et al., 1999; Berg et al., 2004), requiring rapid intervention with anti-epileptic treatment.

Several anti-epileptic drugs (AEDs) are currently available as alternative and competing interventions for treatment of GCSE. However, in the literature most information regarding treatment of GCSE is obtained from clinical trials based on a comparison of one AED with intravenous phenytoin (IV PHT) (Prasad et al., 2005). Such an approach provides only a partial fragment of the whole picture: knowing what is the efficacy and safety of an AED compared with IV PHT may be useful, but ideally one should have the possibility to know how all the different options rank against each other and how big these differences are in effect size between all the available drugs (Brigo et al. 2011).

Randomized controlled trials (RCTs) directly comparing intravenous valproate (IV VPA) with intravenous phenobarbitone (IV PB) are still lacking. Until data from direct head-to-head clinical trials are available, other methods must be used to make comparisons between the new AEDs.

Systematic reviews and meta-analyses of RCTs with similar study designs and using similar methodology are useful, although limited, tools. Classical meta-analyses of RCTs focus on the pair-wise comparison between two treatments (e.g. treatment A versus treatment B), with each included trial providing information for the direct comparison between the two treatments. However, for some treatment direct head-to-head comparisons are not available, and consequently the treatment effect cannot be directly estimated. However, it is possible to estimate the indirect effect of treatment A versus treatment B using evidence from trials comparing tratment A with treatment C, and trials comparing treatment B with treatment C (Tudur Smith et al., 2007). The key assumption for the indirect comparison is that of exchangeability of the treatment effect across all included trials (ICWG, 2009).

The validity of indirect comparisons based on a common comparator (also known as "adjusted indirect comparison", Song et al., 2003, or "common reference-based indirect comparison", ICWG, 2009) depends upon the internal validity and similarity of the included trials (Song et al., 2003). Meta-analyses based on common reference-based indirect comparisons may therefore represent a useful tool where direct comparisons do not exist.

We therefore decided to undertake a systematic review with meta-analysis of IV VPA compared with IV PHT in the treatment of established GCSE in patients of any age, indirectly estimating its efficacy and safety compared with IV PB in a common-reference based indirect comparison meta-analysis.

This protocol will describe the methods and processes used with the level of detail and transparency required to report systematic reviews as described in the PRISMA guidance (http://www.prisma-statement.org/) (Liberati et al., 2009).

SECTION 2: OBJECTIVES

To indirectly compare IV VPA with IV PB in the treatment of established GCSE in terms of:

Efficacy

The proportion of patients with clinical seizure cessation within 30 min after drug administration out of the total number of patients randomly assigned to each treatment arm.

Tolerability and safety
The proportion of patients experiencing adverse effects of any type out of the total number of patients randomly assigned to each treatment arm.

SECTION 3: METHODS

A systematic review involves the systematic and transparent identification, selection, extraction and synthesis of studies relevant to the research question. In this systematic review an approach is being adopted which will facilitate the investigation of indirect comparisons if feasible and required.
The first stage of the systematic review is to define the criteria for considering studies.

Study Selection and Data Extraction

Results of RCTs comparing IV VPA and IV PB against IV PHT in the treatment of GCSE will be included in the meta-analysis using inclusion criteria outlined in Prasad et al., 2005, and Brigo et al., 2012, and based on the method applied by the Cochrane Epilepsy Group. Briefly, we will include include randomized controlled trials, blinded or unblinded. Uncontrolled and non-randomized trials will be excluded. Patients of any age presenting to a hospital or emergency medical departments, and diagnosed with GCSE at any stage, including refractory GCSE, will be included. SE is defined according to Lowenstein as "more than 5 min of (i) continuous seizures or, (ii) two or more discrete seizures between which there is incomplete recovery of consciousness" (Lowenstein et al., 1999). The same diagnostic definition will be adopted for studies on GCSE in children (Shinnar et al., 2001).
We plan to consider separately SE continuing after the 1st line treatment (benzodiazepine, BDZ) from "refractory SE" (SE not responding both to 1st line and 2nd line (another AED, usually PHT) treatment).
We will considered all trials in which IV VPA and IV PB will be compared with IV PHT and which have been included in previously published systematic reviews (Prasad et al., 2005; Brigo et al., 2012). Trials will not be excluded on the basis of dose, duration of treatment, or length of follow-up. No additional data other than those included in these systematic reviews will be added.

Types of outcome measures

We chose dichotomous primary outcomes to have hard outcome measures of both treatment efficacy and safty.
The use of odds ratios for binary outcomes was chosen because it is associated with less heterogeneity in meta-analysis than is the use of risk differences or relative risks (Deeks, 2002).
The following outcomes (reported in studies meeting the inclusion criteria) relevant to the efficacy and safety of the intervention drug (IV VPA versus IV PB) will be collected:

Efficacy
The number of patients with clinical seizure cessation within 30 min after drug administration.

Tolerability and safety
The number of patients experiencing adverse effects of any type.
We also plan to consider mortality among outcomes, provided that a stratified randomization for SE etiology was made (thus ensuring that this extremely relevant clinical aspect was equally distributed in the control and experimental groups) or that enough information on

etiology was reported in the studies, thus permitting a subgroup analysis to relate mortality with SE etiology.

STATISTICAL ANALYSIS

We will use statistical methods in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011) (Higgins and Green, 2011) to measure treatment effect.

For each outcome, an intention-to-treat primary analysis will be made in order to include all patients in the treatment group to which they were allocated, irrespective of the treatment they actually received. The analysis will use intent-to-treat (ITT) data of all randomized patients recorded during the entire treatment period.

Analyses will be be conducted using Revman 5 (conventional meta-analysis for each AED), Excel and R 2.15.1 (common reference-based indirect comparison meta-analysis).

Conventional meta-analysis per AED

A conventional meta-analysis of comparisons between each AED (VPA or PB) and IV PHT will be undertaken. Results from individual trials for each AED (IV VPA and IV PB, each of them compared against IV PHT) will be pooled by using random effects, inverse variance, weighted meta-analysis (DerSimonian and Laird, 1986).

Each outcome will be analysed by calculating odds ratios (OR) for each trial with the uncertainty being expressed using 95% CIs. For each outcome a weighted treatment effect across trials will be calculated. Mantel-Haenszel method will be used to estimate the odds ratio statistic and to combine ORs (Emerson, 1994).

Results of the conventional meta-analysis will be presented in forest plots.

Random effects model

Pair-wise meta-analyses will be performed by synthesizing studies that compare the same interventions using a random effects model (DerSimonian and Laird, 1986) to incorporate the assumption that the different studies are estimating different, yet related, treatment effects (Higgins and Green, 2011). Adjusted indirect comparison using the fixed effect model tend to underestimate standard errors of pooled estimates (Glenny et al., 2005; ICWG, 2009). Thus, the random effects model will be used for the quantitative pooling in both the direct and the adjusted indirect comparison (DerSimonian and Laird, 1986).

Assessment of heterogeneity

Visual inspection of the forest plots will be used to investigate the possibility of statistical heterogeneity. Homogeneity among trial results will be evaluated using a standard Chi-squared test and the hypothesis of homogeneity will be rejected if the P value is less than 0.10.

Assessment of statistical heterogeneity will be supplemented using the I-squared (I^2) statistic which provides an estimate of the percentage of variability due to heterogeneity rather than a sampling error (Higgins et al., 2003).

The interpretation of I^2 for heterogeneity will be performed according to Higgins and Green, 2011. We will assess and discuss possible sources of heterogeneity narratively.

Suitability of indirect comparisons

The suitability of indirect comparisons will be investigated considering whether studies are suitably similar by adopting the framework for assessing exchangeability assumption proposed by ICWG (ICWG, 2009).

Common reference-based indirect comparisons by combining meta-analyses of AEDs

Comparison method

We will conduct a common reference-based indirect comparison meta-analysis, which is a method of synthesizing information from trials addressing the same question but involving different interventions. For a given comparison, say A versus B, direct evidence is provided by studies that compare these two treatments directly. In other terms, for the direct comparisons, comparison of the result of group A with the result of group B within a RCT give an estimate of the efficacy of intervention A versus B. However, indirect evidence is provided when studies that compare A versus C and B versus C are analyzed jointly. Because none of the included trials directly compare IV VPA with IV PB, an adjusted method of indirect comparison between IV VPA and IV PB will be performed using the results of two meta-analyses (e.g. IV VPA versus IV PHT and IV PB versus IV PHT).

Statistical analysis

To perform common reference-based indirect comparisons we will use the method suggested by Bucher (Bucher et al., 1997). By means of this method, the indirect comparison of IV VPA and IV PB will be adjusted by the results of their direct comparisons with IV PHT (common intervention).

This adjusted method aims to overcome the potential problem of different prognostic characteristics between study participants among trials, and it is valid if the relative efficacy of interventions is consistent across different trials. In order for this indirect comparison to be valid, the overall characteristics of the trials included in the meta-analyses should not differ systematically.

The comparison between each AED and other AEDs will be performed using the ORs derived from the meta-analyses.

Comparison of each binary outcome measure will be performed using the log of OR and its variance derived from the meta-analyses (Bucher et al., 1997). The logs of the OR of each meta-analysis are asymptotically normally distributed and statistically independent. The estimate of the treatment effect (i.e. IV VPA versus IV PB) will be therefore calculated by the difference (diff) between the logs of the 2 ORs:

$$\text{Diff} = \ln \text{OR}_{\text{VPA}} - \ln \text{OR}_{\text{PB}}:$$

The 95% confidence interval of this estimated effect will be derived from the standard error of the difference:

$$((\ln \text{OR}_{\text{VPA}} - \ln \text{OR}_{\text{PB}}) \pm (1.96 * \text{SE (diff)}))$$

where $\text{SE (diff)} = (\text{variance } (\ln \text{OR}_{\text{VPA}}) + \text{variance } (\ln \text{OR}_{\text{PB}}))^{1/2}$. Back transformation will be then performed to give the OR and its 95% CIs for the indirect comparisons.

By convention, ORs > 1 indicate that the outcome is more likely in the group receiving IV VPA than in the group receiving IV PHT. The same will be applied for IV PB. For the indirect comparisons, an OR > 1 indicates that the outcome is more likely with IV VPA than with IV PB. A P value of 0.05 will be considered to be statistically significant.

SECTION 4: FINAL REPORT

The content of final report will be detailed according to the PRISMA reporting guidelines (http://www.prisma-statement.org/) (Liberati et al., 2009).

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APPENDIX A: PRISMA FLOW DIAGRAM

Available at:
http://www.prisma-statement.org/2.1.4%20-%20PRISMA%20Flow%202009%20Diagram.pdf

APPENDIX B: PRISMA CHECKLIST

Available at:
http://www.prisma-statement.org/2.1.2%20-%20PRISMA%202009%20Checklist.pdf