Title

INFOMATAS Multi-centre systematic review and meta-analysis individual patient data of dynamic cerebral autoregulation in ischaemic stroke

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Competing interests

None to declare.

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Collaborators

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Abstract

Rationale

Disturbances in dynamic cerebral autoregulation (dCA) after ischaemic stroke (IS) may have important implications for prognosis. Recent meta-analyses have been hampered by heterogeneity and small samples.

Aim and/or hypothesis

The aim of study is to undertake an individual patient data meta-analysis (IPD-MA) of dCA changes post-IS, and to determine a predictive model for outcome in IS using information combined from dCA, clinical history, and neuroimaging.

Sample size estimates

To detect a change of 2% between categories in modified Rankin Scale (mRS) requires a sample size of ~1500 patients with moderate to severe stroke, and a change of 1 in autoregulation index, requires a sample size of 45 healthy individuals (powered at 80%, α 0.05). Pooled estimates of mean and standard deviation derived from this study will be used to inform sample size calculations for adequately powered future dCA studies in IS.

Methods and design

This is an IPD-MA as part of an international, multi-centre collaboration (INFOMATAS) with three phases. Firstly, univariate analyses will be constructed for primary (mRS) and secondary outcomes, with key co-variates and dCA parameters. Participants clustering from within studies will be accounted for with random effects. Secondly, dCA variables will be validated for diagnostic and prognostic accuracy in IS using summary receiver operating characteristic curve (ROC) analysis. Finally, the prognostic accuracy will be determined for four different models combining clinical history, neuroimaging, and dCA parameters.

Study outcome(s)

The outcomes for this study are to determine the relationship between clinical outcome, dCA changes, and baseline patient demographics, to determine the diagnostic and prognostic accuracy of dCA parameters, and to develop a prognostic model using dCA in IS.

Discussion

This is the first international collaboration to use IPD-MA to determine prognostic models of dCA for patients with IS.

Background

Dynamic cerebral autoregulation (dCA) is a key homeostatic mechanism to maintain a constant cerebral perfusion despite systemic fluctuations in blood pressure (BP) and CO_2 (1). dCA can be measured non-invasively by transcranial Doppler ultrasonography (TCD), most commonly using transfer function analysis (TFA) of spontaneous fluctuations in BP (1, 2). A number of excellent reviews have been published on TFA (2, 3), but in brief, TFA uses Fourier decomposition to measure three main properties of autoregulation: gain, phase, and coherence (2). In addition, the autoregulation index (ARI) can also be calculated using the gain and phase frequency responses. Gain describes the frequency dependent ratios in amplitude of the input (BP) compared to the output (cerebral blood flow velocity, CBFv), where higher gain represents less efficient autoregulation (2). Phase shift describes the recovery of changes in CBFv relative to those in ABP, where high phase shift represents more efficient autoregulation (2). Coherence expresses the fraction of output (CBFv) power that can be linearly explained by the corresponding input (BP) power at each frequency. Values of coherence approaching 1.0 result from signals with very high signal-to-noise ratio (SNR) and a strong univariate input-output linear relationship. The 95% confidence limit of the distribution of coherence is normally used to reject estimates of gain and phase where SNR is low, the relationship is non-linear, or there are multiple inputs affecting the CBFv output (2).

Systemic and cerebral haemodynamic perturbations in the acute/sub-acute phase of ischaemic stroke (IS) may affect clinical outcomes (3, 4), with possible correlations with stroke severity (5). Several single-centre TCD studies primarily investigating IS sub-types have increased our understanding of dCA during the acute and chronic phases (3). Unfortunately, prior attempts at data synthesis have failed due to a lack of methodological homogeneity in TCD study design and analysis (3). However, large normative datasets (6), consensus guidelines (2) and multi-centre studies to improve reproducibility of CA estimates (7) are examples of efforts designed to minimise heterogeneity and increase statistical

power. There exist convergent findings demonstrating impairment of CA up to two weeks post IS. Importantly, these findings are demonstrated irrespective of geographical location (8), and the presence of hypocapnia (4). Increased emphasis is being placed on 'dynamic' studies of blood flow during the acute stroke period in an effort to determine the impact of autoregulation guided management strategies on clinical outcome. Concern has been raised about 'intensive' strategies to lower BP, particularly in the presence of presumed impaired autoregulation, as there is the potential for ischaemic harm through cerebral hypoperfusion. The 2nd CARNet Bootstrap Project has pooled data from five different centres (9) , but at present there has been no pooled individual patient analyses with dCA data of IS patients.

Individual patient data meta-analysis (IPDMA) contrasts with traditional methods for meta-analysis by aggregating raw data at the individual patient level, rather than combining study-level data (10, 11). IPDMA is increasingly used in areas previously hampered by significant heterogeneity at study-level, thus improving standardisation of analysis across studies, reducing heterogeneity, and improving reliability of pooled estimates (10, 11). IPDMA can be considered as a one- or two-stage approach, the former uses statistical methods to construct multivariate models, where patients are clustered by study origin using mixed effects modelling (10). In the two-stage approach, data are re-analysed at the individual level and traditional methods are employed to aggregate the data at study level (10). There is an increasing trend in the literature towards the use of one-stage IPD analysis over the traditional two-stage method (12, 13). The one stage approach has been demonstrated recently to out-perform the two stage approach, particularly when investigating interaction effects. In the context of dCA measurements in IS, many of the primary studies are case-control, cross sectional, or cohort in design, with small patient numbers (3). Thus, adjustment for confounders in primary studies is frequently hampered by small sample sizes. A one stage approach would facilitate an adjusted analysis of the role of dCA in IS, and provide important information on which baseline factors are associated with better or worse dCA in IS, and how this relates to prognosis and clinical outcomes.

This analysis has been separated into three distinct phases with the aims as follows:

1. To explore the scope, severity, and temporal changes of dCA impairments in IS, and the relationship with baseline demographics, and neuroimaging and clinical outcome variables
2. To identify the diagnostic test accuracy (DTA) for measures of dCA impairment in distinguishing IS from non-IS, and in predicting outcome
3. To develop a risk prediction model for outcome in IS by combining clinical, neuroimaging and dCA information.

Methods

This protocol has been developed in line with reporting guidelines for IPD analyses (14).

Inclusion criteria

1) Adults aged >18 years

2) Diagnosis of IS (all sub-types)

3) Cerebrovascular parameters available, including indices of dCA (up to twelve months post-symptom onset)

Exclusion criteria

1) Centre declines to participate
2) Significant missing data that will compromise study validity determined by consensus agreement of the INFOMATAS group
3) Low quality studies as per criteria below

Identification of participating centres

Participating centres contributing data analysis will be identified through the Cerebral Autoregulation Network, from recent systematic reviews, and through systematic searching of the literature (search strategy in Supplementary Information I).

Creation of IPD file and confidentiality

All individual patient data will be anonymised prior to sharing between centres and no patient identifiable data will be included. Ethical approval for this study was not sought as no new patient data are being collected, and analyses are similar to those conducted in the original individual trials.

Data exchange

A data use agreement will be in place prior to data exchange. A list of the selected variables which will be shared between centres is shown in Supplementary Information II. A standardised data dictionary will be used by all centres to ensure variables are collected and coded in a consistent manner between centres. The receiving centre will amalgamate the data independently of the analysing centre.

Data quality assurance

Data will be checked at the contributing centre level for accuracy, completion, and integrity. The nomenclature of the files will be standardised between centres prior to analysis. Any data queries or missing data will be resolved through contact with the trial investigators.

Pooled IPD analysis sample

Studies included in the final analysis will be summarised, in terms of inclusion and exclusion criteria, and baseline characteristics.

Primary study quality and risk of bias assessment

The primary studies included in the final analysis will be appraised for quality using CONSORT (15) (randomised), STROBE (16) (observational), QUADAS-2 (diagnostic test accuracy) studies (17), and against the criteria in the CARNet white paper for studies of dCA (2). Two centres will independently

appraise studies and a third centre will mediate disagreements in quality assessment. Risk of bias will be summarised in table and charts.

Baseline dCA variables

In addition to standard parameters used to describe cerebral haemodynamics (mean CBFv, mean arterial pressure, end-tidal CO_2 ($EtCO_2$), heart rate), the metrics adopted to assess dCA will be those obtained from transfer function analysis (TFA) of recordings at rest (coherence, gain, phase, both at very low frequency and low frequency), as well as the autoregulation index (ARI from TFA, thigh cuff or sit-to-stand). The methods used by primary studies to generate these measurements will be summarised.

Baseline co-variates

Co-variates relating to participant characteristics, interventions, and neuroimaging findings recorded at baseline will be included in analyses. A full list of all co-variates and descriptors can be seen in Supplementary Information II.

Outcome variables

The temporal changes in dCA parameters (gain, phase, ARI) will be investigated relative to baseline measurements from the acute phase, where data are available, up to 12 months post-IS. Where available, these differences will be compared to control population data. We will identify which baseline parameters are predictive of poorer dCA in the longer term, and whether this relates to clinical outcome (mRS) using uni- and multivariable analyses as described below.

The primary time point for analysis of primary and secondary clinical and dCA outcomes will be three months, but we anticipate studies will have reported outcomes at different time points and will thus be grouped into time points from symptom onset, where the pathophysiological changes are similar to facilitate analyses: within the first 24 hours, 24-72 hours, 4-7 days, and 3, 6 and 12 months post-event. If possible, the first 24 hours will be further sub-divided into 0-6 hours and 7-24 hours.

The primary outcome for the analysis will be modified Rankin scale (mRS). Secondary clinical outcome measures include: mortality, mRS (dead or dependent (3-6)/independent (0-2)), National Institute for Health stroke scale (NIHSS), Glasgow Coma Scale (GCS), Barthel index, symptomatic haemorrhagic transformation, and infarct size/volume will be collected from the last radiological imaging (MRI or CT) undertaken during hospital stay. A full list of all outcomes and descriptors can be seen in Supplementary Information II.

Missing data

The investigators anticipate the majority of data sets will be complete, however datasets with missing data will be considered for analysis if they meet the quality criteria and will be determined by consensus agreement of the INFOMATAS group.

IPD analysis

Phase 1: Univariable analysis

The primary outcome (mRS) and all other binary or ordinal outcomes will be analysed using Generalised Estimating equations. All continuous outcomes will be analysed using Generalised Linear Mixed Models. All models will consider study the patient originated from as a random effect. All models will consider the co-variates outlined above. Model estimates, standard errors, odds ratios and 95% confidence intervals will be presented where appropriate. Results will be considered statistically significant where $p<0.05$.

Phase 2: diagnostic test accuracy

In the first instance, data will be analysed at study level, and extracted into binary two-by-two tables (binary test results cross-classified with the binary reference standard) to calculate sensitivities and specificities with 95% confidence intervals for each parameter of dCA. For each study, estimates of sensitivity and specificity will be plotted graphically in forest plots and receiver operating characteristic (ROC) curves (RevMan 5). Where there are more than three studies available at the

same test threshold and parameter, summary analyses will be performed using a bivariate random effects analysis, to calculate pooled estimates of sensitivity, specificity, positive and negative predictive values, positive and negative likelihood ratios, with 95% confidence intervals. The test thresholds will be identified through systematic review and through consensus discussion with the INFOMATAS group.

Summary analysis will be performed using MetaDTA (18).

Phase 3: Multivariable modelling and DTA analysis

Using the univariable analysis from phase 1, four models will be constructed to investigate the test properties for each of the dCA parameters when prognostic patient factors are accounted for. The four models will be constructed as follows:

Model 1: clinical history alone
Model 2: clinical history + dCA parameters
Model 3: clinical history + neuroimaging
Model 4: clinical history + neuroimaging + dCA parameters

Each of the above models for different dCA parameters will be represented graphically in a ROC curve, and the accuracy of each model will then be compared from the ROC analysis.

Heterogeneity analyses

Pre-specified heterogeneity, sub-group and sensitivity analyses have been presented in Supplementary Information III.

Sample size

Firstly, to detect a change of 1 in ARI, a sample of at least 45 healthy individuals is required (powered at 80%, α 0.05). We anticipate a loss to follow-up of approximately 10% of the cohort and thus require a sample of at least 65 stroke patients. Secondly, to detect a change of 2% between categories in mRS,

a sample size of approximately 1500 patients is required in moderate to severe stroke (powered at 80%, α 0.05) (19). To date, no study has calculated the required sample size to detect clinically significantly change in dCA parameters in IS, and individual studies have thus far been small, therefore accurate mean and standard deviation values are not known. We plan to use the pooled mean and standard deviation from this IPDMA to undertake sample size calculations for future studies to facilitate adequately powered studies using dCA parameters as outcome measures.

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Figure 1. TFA metrics of gain, phase, and coherence. Courtesy of JD Smirl '*The relationship between arterial blood pressure and cerebral blood flow: insights into aging, altitude and exercise'*, PhD Thesis, The University of British Columbia (Okanagan), June 2015 and published previously (2). MAP: mean arterial pressure; MCAv: cerebral blood flow-velocity in the middle cerebral artery.