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Clinical studies

Thrombolysis in Acute Stroke Pooling Project: a meta-analysis on individual patient data

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Summary To assess the efficacy and safety of thrombolytic therapy in acute ischaemic stroke, randomised clinical trials have been undertaken. Their results suggest that further research should be attempted to identify patients for whom the benefit/risk ratio of thrombolysis is beneficial. The Thrombolysis in Acute Stroke Pooling Project (TAS-PP) group will pool individual patient data from recent studies and meta-analyse these. A Steering Committee drafted the protocol and defined access rules to the common file. The objectives are to assess the efficacy of thrombolysis to reduce death or severe disability, to identify predictors of death and haemorrhagic transformation, and to identify subgroups with a better response to treatment, using logistic regression, survival curve comparison (log rank test), multivariate modelling (with treatment, baseline characteristics, delay from symptom to treatment as covariates). This project will help defining subpopulations that are more likely to benefit from this treatment, which cannot be achieved using tabulated data, and designing future trials.

Keywords: meta-analysis, individual patient data, thrombolytic therapy, cerebral ischaemia, acute disease

INTRODUCTION

Stroke is a major health problem in developed countries. It is the third most common cause of death and the major cause of disability in adults. Cerebral infarction accounts for about 80% of strokes. There is, to date, no effective and safe treatment which improves prognosis in a clinically significant magnitude after cerebral infarction, and therefore, clinical trials aimed at evaluating drugs that could reduce the mortality rate and residual disability are of major importance. Thrombolytic agents promote early recanalization resulting in reperfusion of ischaemic regions, thus leading to a reduction of the volume of infarction in animals. In humans, clinical studies of thrombolysis in ischaemic stroke have been published in the 1960s to 1970s, and a preliminary meta-analysis using the published data from randomized trials involving 600 patients in total with previous computed tomography (CT) scan[1] showed an encouraging non-significant 37% reduction in the total mortality rate (95% confidence interval, 74% reduction to 40% excess) and a significant 56% reduction in the rate of mortality or deterioration (95% confidence interval, 20–70% reduction). The studies were heterogeneous in design, delay from stroke onset to treatment, dose and type of thrombolytics (in only three the treatment dose was sufficient to permit early recanalization). The rate of haemorrhagic transformations was not available for all studies or all treatment groups. More recently, large randomized clinical trials have been published.[2–7] In these trials, the thrombolytic agent was administered intravenously after a CT scan within a maximum of 6 h after the onset of symptoms. The clinical endpoints were the case fatality rate and disability, as assessed using the Rankin scale and/or Barthel scale[8] measured at 3 or 6 months. The main characteristics of the trials are summarized in Table 1. Three of these trials were stopped early for safety reasons (Multicentre Acute Stroke Trials–Europe (MAST–E), Multicentre Acute Stroke Trials–Italy (MAST–I) and Australian Streptokinase Stroke Trial (ASK) (group 3–4 h), whereas the European Co-operative Acute Stroke Study (ECASS) and the National Institute of Neurological Diseases and Stroke trial (NINDS–tPA) reached the planned recruitment.[6,9–11] All but the NINDS–tPA trial showed a non-significant increase in the total mortality mainly due to cerebral haemorrhages, and a non-significant trend towards a slightly better functional outcome (intention-to-treat results). Therefore, there is a hope that a selection of patients with a better outcome could be possible (e.g. in those without severe hypodensity on their baseline CT scan assessment). Neurologists are currently faced with the dilemma of performing further research on thrombolytic therapy in acute ischaemic stroke without exposing more patients to these treatments (which have been shown harmful to date). A group formed before the above studies were started designed the Thrombolysis in Acute Stroke-Pooling Project (TAS-PP) and decided to pool the individual patient data from these trials. The main objectives are to identify patients who could most benefit from thrombolytic therapy or who are at greater risk of haemorrhagic transformation, and to identify predictors of haemorrhagic transformation. The only way to achieve this in the present scientific context is to pool the results in a meta-analysis of individual patient data and use multivariate analytic techniques.[12] A recent update of the systematic review of evidence on thrombolytic therapy for acute stroke was limited by the use of tabulated data, because of the heterogeneity between trials[13] for several important characteristics. For example, patients who were treated early were largely those from the NINDS–tPA trial, who also had the better prognosis in the placebo group. Univariate subgroup analyses performed on tabulated data cannot dissociate the trial effect, the effect of the delay from onset of symptom to treatment, and the effect of the baseline prognosis of patients. This paper describes the TAS-PP.

Meta-analysis is a method developed for combining the results from several similar randomized clinical trials, even if their results are apparently conflicting. It allows a precise estimate of the treatment effect based on clinical outcomes and not on intermediate ones. Questions not initially asked in the individual trials may be addressed and new hypotheses to be tested in future trials can be generated. Meta-analyses are commonly performed on summary data extracted from published clinical trial reports, but this approach has some limitations:[12]

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1. publication bias (i.e. 'negative' or non-conclusive trials are less likely to be published than positive ones)[14–17]
2. the number of events in each group are not always presented
3. continuous variables are often categorized
4. treatment effect can be expressed differently between trials
5. baseline characteristics may not be very detailed and/or consistent between trials
6. results are not always analysed using intention-to-treat.

Some of these limitations can be overcome by pooling the individual patients' data. Several examples of this approach in other medical fields have been published.[18–26] Publication bias is reduced because collecting data from all trials implies direct contact with trialists who might be aware of other planned, ongoing or terminated trials. It could be argued that pooling data from unpublished trials could involve a risk because their scientific value has not been assessed through peer review. However, obtaining the trial protocol and the individual patient data enables thorough checking of both the data and the trial design, which is even better than peer review of a trial report submitted for publication. The individual patient data pooling makes it possible to verify the effectiveness of the randomization process and permits adjustment of baseline characteristics thus reducing the consequences of imbalance between the treatment groups. The weighting of trials can be based not only on the size of the trials, but can also take into account differences between the trials. The common file is constituted with a core of major variables of each trial, which permits powerful subgroup analyses, post-hoc stratification and multivariate analyses. Intention-to-treat analyses can be performed while preserving the original randomization and avoiding systematic biases that may result from the selective or differential withdrawal of high risk patients from one group or another. This method for subgroup analysis allows better application of the results of clinical trials for future patients. In addition, event dates are available in the common file which permits the performance of survival statistics, and to estimate precisely the evolution of the risk and the effect of treatment over time. The greatest disadvantage of such a meta-analysis is probably its difficulty, because it is an awesome task to convince trialists to pool their data. Central collection of data, checking and analysis requires a large amount of time.[27] However, it offers many advantages, since once the trialists have been contacted directly, their reluctance has been overcome and a dialogue has been established, it offers good working conditions, with a true collaborative spirit. Prospective meta-analyses in which common outcomes and variable definitions are agreed to before data is collected could be useful in reducing this inter-trial heterogeneity. This approach requires that the trialists establish contact before the initiation of the trials, or at least before completion, to ensure that a common core data set is collected, as in TAS-PP.

OBJECTIVES

The objectives of TAS-PP include both efficacy and safety assessment. For efficacy the objectives include assessing the effect of thrombolytic on the risk of death and severe disability and, secondarily, on all-cause mortality for scheduled follow up (generally between 3 and 6 months) and 1 year all-cause mortality and disability. For safety the objectives include evaluating the risk of early death and haemorrhagic transformation, and major cerebral oedema. Another objective is to study interaction between main baseline prognostic factors (age, delay from onset of symptoms to treatment, initial severity, stroke topography, type of thrombolytic agent, early CT scan assessment findings, use of aspirin or other associated treatments, etc.) and treatment on the risk of death, symptomatic haemorrhagic transformation, and major cerebral oedema.

METHODS

Identification of trials

The eligible trials were identified by searching prospective clinical trials registries such as the International Society of Thrombosis and Haemostasis Registry, the Ottawa Stroke Trials registry, and the Major Ongoing Stroke Trials Registry, by contact with the Cochrane Collaboration Stroke Review Group, by electronic database searching (MEDLINE), hand-searching conference abstracts and direct contacts with trialists who were involved in designing trials in acute stroke.[28–32]

Selection criteria for the inclusion of trials in TAS-PP

The selected clinical trials had to:

1. be controlled trials
2. be randomized (with a precisely described randomization process ensuring that the next treatment cannot be guessed)
3. include more than 10 patients
4. use a thrombolytic treatment in the acute phase of ischaemic stroke (within 6 h or less of symptom onset), at a dose which could be expected to achieve recanalization
5. require a CT scan assessment prior to inclusion and exclude patients with signs of haemorrhagic stroke from treatment.

Procedures for data collection and quality control: after completion of the trials, each data file will be added to the common file, as soon as the trials' Steering Committee agree to do so (in the majority of cases, once the main trial results have been accepted for publication). Technically, the trialists can supply data in any computer format, provided that both the files and variables are clearly described. A common core of data (Table 2) will be extracted from each study file and pooled in the common file. Data will be checked for accuracy, consistency and the efficacy of the randomization, and the completeness of the follow up will be controlled. The trial's representative will be asked to verify the data.

Anticipated problems

The different neurological scales used for patient assessment at baseline (Table 1) might limit the possibilities of adjustment on baseline severity. Some of these scale are easily compatible, but comparison between the National Institutes of Health (NIH) stroke scale and the others may be more difficult.[33] Severity at entry will be assessed using the item 'consciousness' of each study as a categorical variable, i.e. 'alert' or 'coma'. The primary outcome in all trials is a combination of death and disability as judged using the Barthel[8] and/or Rankin scale. A correspondence between both scales will be possible since both scores are available in some trials. The other variables that are different, e.g. delay from onset of symptoms to treatment, different age limits or cerebral territory, can be included in the analysis as covariates.

Strategy for the statistical analysis

The statistical analysis will be conducted following the intention-to-treat principle (i.e. all patients will be analysed in the treatment group to which they were randomized). Baseline population characteristics will be described by trial and overall in the two treatment groups. The trial populations will be examined to identify any heterogeneity. The primary outcome for efficacy will use a combined criteria (Rankin scale ≥ 3 or death). A log rank test stratified on the trials will compare survival between the active and the placebo group, with censoring defined as the date of death, the date of end of follow up period or the date of end of trial,

Table 1 Differences between recent thrombolysis studies in acute ischaemic stroke

Study (number of patients)	Tested drug (dose)/ Control treatment	Delay symptoms to treatment (h)	Types of ischaemia	Main exclusion criteria	Baseline assessment	Follow-up (months)
ASK (322)	SK (1.5 M U**)/Placebo	4	All types	Mild deficit and severe coma	MCANS	3
ECASS (620)	rt-PA (1.1 mg/kg)	6	MCA	Mild deficit and severe coma	SSS, NIH SS	3
Glasgow study (20)	SK (1.5 M U**)/Placebo	6	MCA	> 80 years	SSS, NIH SS	13 weeks
MAST-Europe (310)	SK (1.5 M U**)/Placebo	6	MCA	Mild deficit	MAST-Score*	6
MAST-Italy (622)	factorial design : SK (1.5 MU**)/ aspirin (300 mg)/no treatment	6	All types	Coma	MAST-Italy neurological assessment	6
NINDS t-PA stroke trial (291 + 333)	rt-PA (0.90mg/kg)/ Placebo	1.3 (group 1) 3 (group 2)	MCA	Mild and very severe > 80 years	NIH SS	3–30

SK = streptokinase; rt-PA = recombinant tissue plasminogen activator; MCANS = middle cerebral artery neurological scale; SSS = Scandinavian stroke scale; NIH SS = National Institutes of Health stroke scale.
*a combination of MCANS, SSS and Orgogozo scales, **Million Units.

Table 2 Minima common core of data to be collected in trials participating in TAS-PP

Identification	- date of birth, sex, - onset of symptoms, randomization, (date and time)
Severity and clinical status at baseline	- consciousness, clinical syndromes (MCA total, MCA partial, ACA, PCA, vertebrobasilar, lacunar infarct) - clinical scale* (Canadian Neurological Scale, NIH Stroke Scale, Scandinavian Stroke Scale., MAST-E Stroke Scale) - SBP, DBP, atrial fibrillation
CT scan findings at baseline	- early signs
Compliance	- treatment administration (date, time, completeness)
In-hospital events	- clinical deterioration, date, time, CT after deterioration (yes/no), cause (new infarction, haemorrhagic transformation) - non-cerebral bleeds (severity, date, time)
Second CT scan	- performed (yes/no), date, results (haemorrhagic infarction, infarct intraparenchymal haematoma, haematoma in other territory)
Concomittant hospital treatments	- aspirin, IV heparin, SC heparin, oral anticoagulants, other antithrombotics (specify, date and time started)
Follow up (at 3, 6 and 12 months)	- date of the final follow up (or death); status, Barthel score, Rankin score on that date
Deaths	- date, time, cause: ischaemic stroke, cerebral bleed, massive brain oedema, vascular (myocardial infarction, non-cerebral bleed), non-vascular (accident, suicide, cancer), unknown - confirmed by CT (yes/no), autopsy performed (yes/no)

*score available at randomization; CT = computed tomography; MCA = middle cerebral artery; ACA = anterior cerebral artery; PCA = posterior cerebral artery; SBP = systolic blood pressure; DBP = diastolic blood pressure.

whichever came first. The variation of the treatment effect will be described and modelled in successive time intervals (0–5 days, 5–10 days, 10–30 days, over 30 days). The period at risk to be considered for cerebral haemorrhage with clinical worsening will be the in-hospital follow up period. The proportion of this outcome will be compared between the two groups using a logistic regression with treatment and trial as covariates. The interaction between baseline characteristics of patients and the treatment effect will be investigated by multivariate modelling (logistic regression), to identify subgroups of patients in which the treatment could be more effective (or more deleterious).

Study organization

Before all trials were completed, the TAS-PP Working Group was constituted with representatives from all the on-going or terminated eligible trials. Comparing the protocols and the case report forms from the different trials, the Working Group identified any differences and possible sources of heterogeneity. The Working Group then became the Steering Committee for the project. This Committee is responsible for drafting and finalizing the protocol and plan for analysis, establishing rules regarding access to the common data file and publications, deciding on the extension of the project and approving further analyses. The common data file will be held at the Data Handling Unit in the 'Service de Pharmacologie Clinique', Lyon, France, which has previous experiences in this type of project.[34,35] This unit is responsible for the data pooling, constitution and updating the common file, checking data and running the analyses, for maintaining confidentiality and security of the data files. A copy of the common file will be available for the trial representatives, once the planned analyses have been performed. The Data Handling Unit will write and submit analysis reports to the Steering Committee and prepare publications. The secretariat of the project will be located at the data handling unit.

CONCLUSION

Meta-analyses using individual patient data are increasingly being performed. They offer a reliable means of assessing and quantifying the treatment effect, with fewer bias and more appropriate analyses than meta-analyses performed on summary data. In the specific medical field of thrombolytic treatment for acute stroke, this exercise will be of particular importance to permit adjustment

on covariates which could be confounders in the assessment of treatment effect. The positive results of the NINDS–tPA trial could be due to the type of treatment used (tPA instead of streptokinase), to the dose used (e.g. 0.9 mg/kg instead of 1.1 mg/kg in ECASS), to the shorter delay from onset of symptom to treatment (e.g. fewer than 3 h instead of up to 6 h in the other studies). A different selection of patients between studies could also have decisively influenced the study results, since the patients in the placebo groups had a very different prognosis according to the study. It is therefore essential that all covariates (including type of treatment, trial, dose, delay, severity of deficit at entry, concomitant aspirin treatment and early CT scan signs of parenchymal abnormalities) are included in the analysis, using multivariate modelling, to assess the effect of one covariate, while taking into account the others, thus avoid condounding. This strategy is also the only available method to permit identifying subgroups of patients who could benefit from a thrombolytic treatment. The excess risk of death associated with the treatment can be high and it is a challenging goal to urgently produce more scientific evidence without taking additional risks for patients. Because there are similarities between the trials, and because the constitution of a Working Group occurred some years ago, we might achieve this goal very quickly.

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