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PART II
ROUND TABLE: CEREBRAL ISCHEMIA AND CLINICAL HAEMORHEOLOGY

# ITALIAN ACUTE STROKE STUDY HEMODILUTION(I.A.S.S.-H.)-ORGANISATION AND METHODOLOGY

Italian Acute Stroke Study Group
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ABSTRACT

The Italian Acute Stroke Study Hemodilution (I.A.S.S.-H.) recruits 1,200 patients with recent ( 12 hrs) acute stroke admitted to university-hospital departments of neurology in Italy. The patients, randomized centrally by telephone, are allocated as ollows: 50% to the treated group (hemodilution treatment) and 50% to the control group (standard treatment). Randomization is stratified by centers and severity of neurological deficit on admission.
Hemodilution treatment is performed by venesection and infusion of dextran 40; standard treatment will be provided by each Center within a common general regimen.
At the end of six months the Clinical Coordination Center collects the follow-up data on mortality and disability by telephone. Hemodilution treatment will be considered of benefit if it reduces significantly mortality and disability risk, compared with the control group.

## INTRODUCTION

In experimental focal brain ischaemia, hemodilution has been shown to increase blood flow and preserve cellular iom homeostasis (1,2). Previous clinical trials in patients with ischemic stroke have involved the administration of dextran-40 (3,4,5). The results are controversial.

A recent clinical trial combining dextran and venesection had

KEY WORDS: acute stroke - clinical trial - hemodilution

presented favourable preliminary data (6).

The present multicenter controlled clinical trial was undertaken to evaluate whether early normovolemic hemodilution (within 12 hours) reduces disability and mortality rate after ischemic stroke.

This paper describes the methods employed in the study.

## METHODS

### 1. Organization and Sample Size

This is a prospective, controlled multicenter trial involving stratified randomization. Table 1 shows the main organizational aspects. 50% of the patients admitted to the study are treated with hemodilution and 50% with standard treatment only.

Allocation to one of the two groups is made by telephone according to a central randomization list.

Randomization is stratified within each center and within entry severity groups (presence or absence of coma).

The study is not blind, but the end points evaluated in the analysis (mortality and disability) are collected blindly with respect to the treatment groups.

The required sample size and duration of follow-up have been determined on the basis of the following estimates and specifications: a) for control group patients an expected combined severe disability and death rate of 50% over six months; b) for hemodilution-treated patients an estimate 20% reduction of severe disability and death rate over six months; c) a value of alpha and beta respectively of 0,05 and 0,05.

### 2. Patients Eligibility

All patients hospitalized for focal neurologic deficit due to cerebrovascular disease are eligible. A list of these patients is drawn up including their full name, sex, age and reason for exclusion if any.

The following patients are excluded: 1) patients with a previous history of cerebral stroke with residual neurological deficit; 2) patients who cannot be randomized within the first 12 hrs of illness; 3) patients in whom the neurological deficit has resolved completely by randomization; 4) patients in coma, without evidence of unilateral motor deficit; 5) patients with subtentorial lesion (bilateral or alternate motor or sensory deficit, cerebellar deficit of more than one cranial nerve except for nerves VII and XII if associated with homolateral motor deficit; 6) patients with hematocrit of 35% or lower; 7) patients who will present medical problems which may interfere with hemodilution.

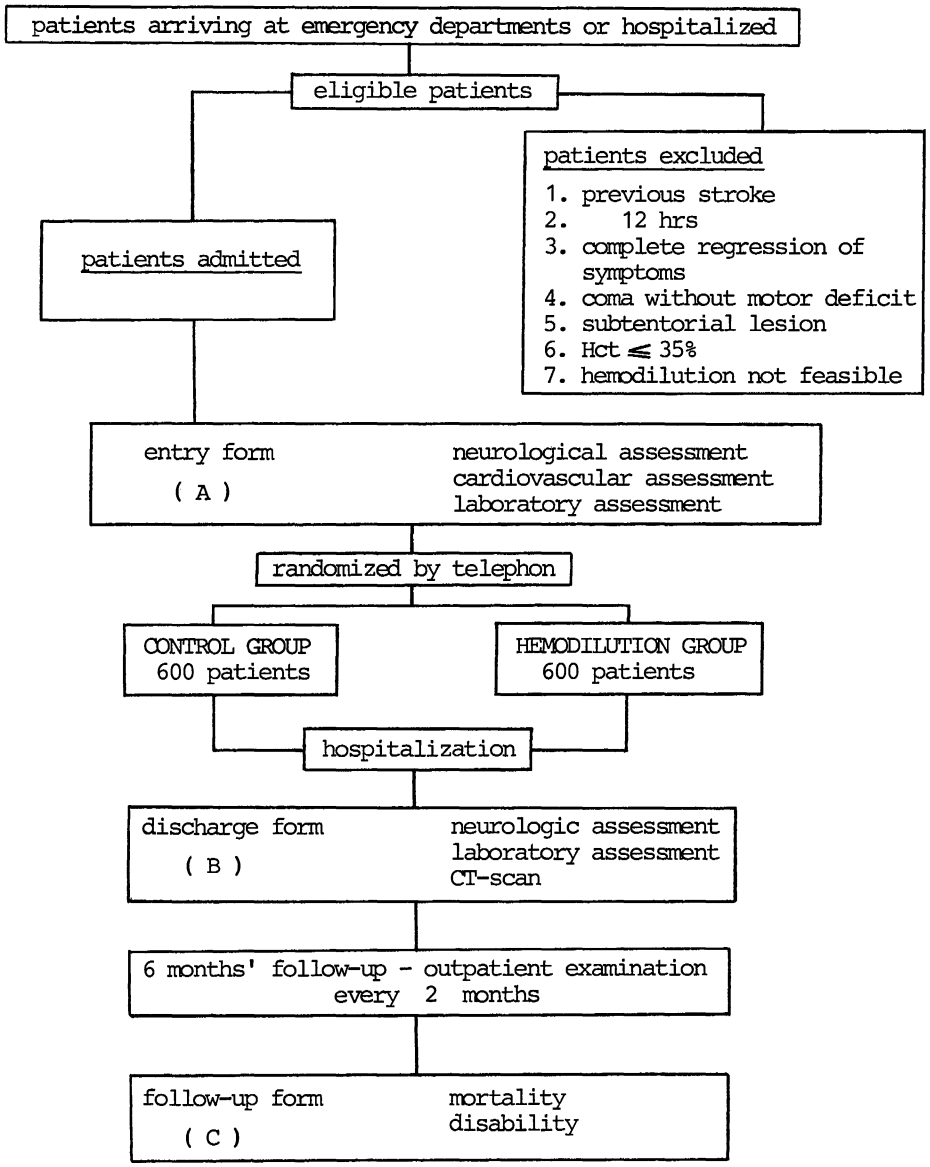
Patients (or family member) are informed orally whenever possible and informed consent is requested.

### 3. Treatment

In patients assigned to hemodilution therapy 350 ml dextran-40 saline (Rheomacrodex$^{R}$) was infused, followed - ten minutes after start - by venesection 350 ml. Hematocrit is determined

TABLE 1

Trial Organisation



again in the 6-12 hours and in the 12-24 hours following respectively the first and second treatment. 350 ml dextran-40 and 350 ml venesection will be repeated (maximum twice) in the patients who still have a hematocrit of over 35%. The patients in the control group receive standard treatment only, since it is not possible to make use of sham procedures. The following indications regarding general treatment are provided in order to standardize the treatment as much as possible in both groups: fluid and electrolyte balance and cardiocirculatory conditions to be controlled; arterial blood pressure to be kept within the mean values before the stroke; heparin calcium to be used at prophilactic doses for patients at high risk for deep vein thrombosis (DVT) (obese, hemiplegic, previous episodes of DVT); specific antiedema treatment (mannitol, glycerol etc.) to be used on patients with rostrocaudal deterioration of consciousness.

The patients allocated to the hemodilution group in whom the treatment is not performed or is suspended, are included in the treatment group for statistical evaluation of the results in accordance with the intention-to-treat principle.

4. Baseline Investigation

Neurological evaluation is carried out and recorded on standardized form at entry. The severity of neurologic deficit is classified in 5 levels: 1) coma; 2) stupor; 3) severe motor deficit; 4) slight motor deficit; 5) other neurologic deficit without motor deficit. The patient's blood pressure, heart rate, rythm and presence of atrial fibrillation are recorded. Hematocrit is determined at entry, and repeated 6-12 hours later, 12-24 hours later and each day for the first seven days of hospitalization. Plain CT-scan is performed as soon as possible, not later than the second day, in order to obtain a reliable differential diagnosis between ischemic and hemorrhagic lesion. Alternatively, autopsy may be used for this purpose.

5. Follow-up And Events

All patients (or family member) are interviewed after six months by telephone. Data and causes of death or disability status in survived patients are collected. The assessment of disability status is performed according to a standardized scale modofied by Garraway (7).

## CONCLUSION

Our major concern in conducting this multicenter clinical trial is to treat very recent strokes, before irreversible brain damages occur. In fact the interval of time between onset of symptoms to randomization is less than 12 hours. This time is too short for a complete clinical and diagnostic evaluation and the patients introduced in the study are, actually, very unselected. In order to obtain significant difference in prognosis between treatment and control groups the protocol is designed to include a large number of cases.

A different policy would be to organize a more restricted clinical trial on very selected patients with objective measurement

of parenchymal ischemic damage. But I wonder whether at the moment an objective evaluation of treatment effect, other than the clinical one, is possible.

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## APPENDIX

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