Glycerol and Dextran Combined in the Therapy of Acute Stroke

A Placebo-Controlled, Double-Blind Trial With a Planned Interim Analysis

A. Frei, C. Cottier, P. Wunderlich, and E. Lüdin

Although the incidence of stroke is declining in Western societies, it is still a major cause of morbidity and death. Early mortality is reported to be 30%, and 1 out of 2 survivors suffers from permanent disability. The majority of strokes are due to atherothrombotic brain infarction or cerebral embolism. Our understanding of the pathophysiology of acute cerebral ischemia has improved considerably in recent years. Based on this knowledge, various therapeutic strategies have been developed to preserve the integrity of nerve cells and to prevent the accumulation of toxic metabolites. Substances such as glycerol or steroids have been shown to decrease edema formation, and anticoagulants and platelet antiaggregation drugs impede thrombosis. In experiments, the hemorrheologic effects of dextran and other maneuvers to lower blood viscosity have improved regional cerebral blood flow. Presently drugs influencing cell metabolism such as prostacyclin or calcium channel blockers are being evaluated.

The results of clinical trials that have investigated the effect of glycerol or dextran in acute stroke have been inconsistent. The effect of glycerol therapy and a combination therapy of glycerol and dextran was evaluated in a double-blind, placebo-controlled study. Repeated neurologic examinations (Day 0, Weeks 1, 6, 12, and 24) according to a modified Mathew score were performed on 62 patients. Statistical analysis showed no superiority of either treatment compared with placebo in acute ischemic stroke. A retrospective estimation of the Type II error of the study yielded approximately p = 0.25. A major side effect was hemolysis in 98% of patients treated with glycerol.

The University Hospital is the only medical facility in Basel that offers 24-hour emergency service. The majority of patients suffering from acute stroke within the city limits are therefore admitted to this institution. Every eligible patient not excluded by the criteria above was seen by the investigators. Informed consent was obtained from the patient, or in the case of aphasia, from the closest relatives. A thorough neurologic and medical examination was performed, and a neurologic score was determined. The score consisted of a modified Mathew scale and was based on observations of the following neurologic functions (maximum score for normal function in parentheses): 1) degree of general incapacitance (28), 2) motor and sensory control of speech (23), 3) motor control of extremities (20), 4) state of consciousness (8), 5) visual function (6), 6) orientation (6), 7) function of facial nerve (3), 8) tendon reflexes (3), 9) sensory function of the extremities (3). If a subject died, the score was 0; the maximum total score was 100.

Routine laboratory analysis included serum electrolytes, creatinine, and liver function tests (GOT, GPT, alk Ph, bilirubin), prothrombin time, blood cell counts, reticulocyte count, and other measures of hemolysis (serum LDH, free hemoglobin, haptoglobin, and urinary hemoglobin). A chest x-ray and an ECG were done in every subject, and a brain CT scan was performed on admission and usually on Day 6. The CT scan was recorded on a EMI 100010, slice thickness 10 mm, and analyzed by visual assessment.
Patients were randomly assigned to 3 treatment regimens: Group 1 (GLY): glycerol 10% 500 ml over 4 hours i.v. followed by placebo (glucose 2.5% + sodium chloride 0.45%); Group 2 (GLY + RHEO): glycerol 10% 500 ml over 4 hours i.v. followed by dextran 50 g and dextrose 25 g (Rheomacrodex) 500 ml over 3 hours i.v.; Group 3 (PL): placebo 500 ml over 4 hours i.v. followed by placebo 500 ml over 3 hours i.v. The regimens (1, 2, or 3) were infused on a double-blind basis daily from Day 1 to Day 7 after hospital admission, starting 24–32 hours after the appearance of the first symptoms of stroke. Patients in the GLY + RHEO group received 20 ml hapten i.v. preceding the first infusion; the other patients received 20 ml isotonic sodium chloride. Between Day 1 and Day 7 urinary volumes, serum creatinine, and the parameters for hemolysis were determined regularly. Infusion treatment was stopped when a state of coma, cardiac failure not readily responsive to diuretics, or renal failure developed. The physician in charge of the patient was free to choose whatever medication he thought indicated, such as digitalis, diuretics, platelet antiaggregation drugs, etc. All patients were routinely engaged in physiotherapy.

The neurologic examination was repeated at 7 days, 6, 12, and 24 weeks after admission by the same investigator and the results were expressed in the neurologic score explained before. This study was approved by the ethics committee of the University of Basel Medical Faculty.

**Study Design and Statistical Analysis**

The study was designed as a double-blind randomized controlled trial. For random assignment of the treatments, the patients were stratified by age (< or > 65 years), sex, and presence or absence of diabetes mellitus. For ethical reasons a group sequential design was chosen in which interim statistical analysis is carried out and the study stops as soon as one treatment can be established as superior. In the present study, one interim analysis with 100 patients and a final analysis (if necessary) with a total of 200 patients was planned. The principal measure of treatment success was the difference between the neurologic score on the day of entry and after 6 weeks. These differences were not normally distributed, and therefore a rank test was used for significance testing (Benard and van Elteren's generalization of Friedman's test for block designs). The significance level of the two tests (one interim and one final test) was set at α = 3% to achieve the usual total Type I error of 5%. The power of the study, i.e., the probability of statistical significance, for a clinically relevant treatment effect was estimated to be about 80% assuming that a relevant superiority of one treatment should lead to a mean treatment success of at least 10 points better than that of the other treatments.

The data were analyzed on an intention-to-treat basis. Patients who died or were excluded for heart failure or development of coma between Day 0 and Day 7 scored 0 points on Day 7, and Weeks 6, 12, and 24. For patients who died after Day 7 (or were excluded during the trial), the last score prior to this event was used for the following examination dates. A subject who died on Day 31 and had scored 43 points on Day 0 and 65 points on Day 7 would score 65 points also at Weeks 6, 12, and 24. Significance tests for possible relations between neurologic function and other clinical observations were carried out only in an exploratory sense. These tests (U test, χ² tests, and Fisher's exact test) were calculated with the software package SPSS-X.

**Results**

Between May 1982 and March 1984, 61 patients with acute stroke and hemiplegia entered the study. Table 1 describes the baseline characteristics. There were 41 men and 20 women. Sex and age were not statistically different between the 3 treatment groups. The youngest subject was 45, the oldest 80 years old; 11 patients suffered from diabetes mellitus (2 were on insulin), 7 had a history of arterial hypertension, and 18 a history of coronary heart disease with signs of myocardial infarction in the ECG. Peripheral atherosclerotic occlusive disease was found in 11, atrial flutter in 14 subjects. The incidence of these concomitant diseases did not differ significantly between the 3 treatment groups.

Table 2 presents the median neurologic score for each treatment group at hospital admission (Day 0), Day 7, Weeks 6, 12, and 24. The median scores on Day 0 did not differ significantly between the 3 groups. Figure 1 presents the median change in score between Day 0 and successive examinations, and Figure 2 gives the change in scores between Day 0 and Week 6 for each subject individually as well as the median for the group. The rank test was applied to this comparison of the changes in score between Day 0 and

<table>
<thead>
<tr>
<th>Age (years, mean ± SD)</th>
<th>Glycerol + Placebo</th>
<th>Glycerol + Dextran</th>
<th>Placebo + Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>(range)</td>
<td>(56–76)</td>
<td>(45–76)</td>
<td>(53–80)</td>
</tr>
<tr>
<td>Men</td>
<td>12</td>
<td>15</td>
<td>14</td>
</tr>
<tr>
<td>Patients with</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>5</td>
<td>4</td>
<td>4</td>
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<tr>
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<td>3</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>7</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Atrial flutter</td>
<td>4</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Peripheral atherosclerotic occlusive disease</td>
<td>2</td>
<td>3</td>
<td>6</td>
</tr>
</tbody>
</table>

| Neurologic score (median ± SE) | 62.5 ± 9.2 | 55.0 ± 7.5 | 55.5 ± 5.1 |
Table 2. Neurologic Scores

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Glycerol + placebo</th>
<th>Glycerol + dextran</th>
<th>Placebo + placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 18</td>
<td>62.5 ± 9.2</td>
<td>61.0 ± 11.1</td>
<td>55.0 ± 5.1</td>
</tr>
<tr>
<td>n = 23</td>
<td>70.0 ± 7.1</td>
<td>78.0 ± 13.9</td>
<td>71.0 ± 6.4</td>
</tr>
<tr>
<td>n = 20</td>
<td>71.5 ± 7.2</td>
<td>71.0 ± 11.0</td>
<td>75.0 ± 8.6</td>
</tr>
</tbody>
</table>

Data are median ± SE of medians calculated by the bootstrap method, see Efron.41

Week 6; Figure 1 shows that most of the neurologic recovery took place during this period.

Ten of the 61 patients (16%) who entered the study died during the trial. Between Day 0 and Day 6, 1 patient died in the GLY and 1 in the GLY + RHEO group; both had complete occlusion of the middle cerebral artery and severe brain edema at autopsy. Between Day 7 and Week 6, 1 patient died in the PL group from pulmonary embolism, 5 patients died in the GLY and GLY + RHEO groups (2 from myocardial infarction and 1 from pulmonary embolism; in 2 patients the cause remained uncertain as autopsy was not performed). Two patients in the GLY group died after Week 6. Three patients discontinued infusion therapy in the first week: 1 in the GLY and 1 in the GLY + RHEO group for left heart failure, and 1 in the GLY group due to coma; this patient later regained consciousness. All other patients were followed over 24 weeks.

The number of patients entering the study was lower than expected; therefore, an interim analysis was performed using all the information obtained for 52 patients. This analysis showed only minimal differences in treatment success between the 3 groups. In the frame of Bayesian statistics, a posteriori distributions for treatment effects were calculated using so-called vague a priori distributions (according to Jeffrey's rule31) and the experimental data for the 52 patients. To simplify calculations for this crude estimation, normal distributions were assumed. The probability of eventually achieving experimental significance with a total of 200 patients was then easily calculated and yielded a chance of only 6%. This led to the decision to stop the trial after only 61 patients had been included.

Probably due to the small sample size, outcome (change in neurologic score between Day 0 and Week 6) showed no relation to preexisting arterial hypertension, diabetes mellitus, coronary heart disease, atrial flutter, or peripheral atherosclerotic occlusive disease. There were no significant differences in the use of digitalis, diuretics, platelet antiaggregation drugs, anticoagulants, and calcium channel blockers between the 3 study groups.

The mean drop in hemoglobin for the 41 patients treated with GLY or GLY + RHEO was 1.7 ± 1.2 g%; the maximal fall in hemoglobin was 5 g%. Ninety-eight percent of all patients treated with glycerol showed signs of hemolysis, serum haptoglobin <0.5

![Figure 1](http://stroke.ahajournals.org/)

**Figure 1.** Change in neurologic score from Day 0 to Weeks 6, 12, and 24 (median ± SE; SE calculated by the bootstrap method, see Efron41).
and 3 of the following criteria: serum free hemoglobin > 10 mg/dl, LDH > 250 IU, urinary hemoglobin > ++, and reticulocytes > 15%. No incidence of allergic reaction to dextran 40 (Rheomacrodex) and no serious impairment of renal function was observed.

Clinical evidence for deep vein thrombosis between Day 0 and Week 6 was found in 33% of the patients in the PL, in 12.5% of the GLY, and in 4.5% (p < 0.05 vs. PL) of the GLY + RHEO group.

Nineteen patients showed no hypodensity in the CT scan done on Day 6 and had improved by 17.3 ± 13.7 points in the neurologic examination at Week 6. As expected, patients with hypodense areas in the CT scan on Day 6 (68%) had improved less at the Week 6 neurologic examination, by only 9.1 ± 18.8 points.

**Discussion**

A number of medical, therapeutic measures have been used in the attempt to improve neurologic function after completed stroke. Glycerol may reduce cerebral edema and increase regional cerebral blood flow after occlusion of a cerebral artery in animal experiments and in man; furthermore, a beneficial metabolic effect on neural cell metabolism has been suggested. Dextran (such as Rheomacrodex) has been shown to improve regional cerebral blood flow by hemodilution, probably by reduction of platelet aggregability and other effects that lower blood viscosity. In theory, the combination of both these therapeutic principles should be superior to the use of each substance alone. We therefore compared the effect of glycerol alone (GLY) to glycerol and dextran combined (GLY + RHEO) in a prospective double-blind placebo (PL)-controlled trial. As presented in Table 2 and Figures 1 and 2, we could not show a beneficial influence of GLY or GLY + RHEO on recovery of neurologic function after acute stroke.

Figure 1 demonstrates that most of the recovery in neurologic function took place within the first 6 weeks after cerebral infarction. For that reason the principal
test for statistical significance (Benard-van Elteren rank test)\(^{23}\) was applied to compare median changes in neurologic score between Day 0 and Week 6. We did not calculate the outcome for patients with little, intermediate, and severe neurologic deficit separately as other authors have done\(^ {18,21,22,24}\) since this mode of analysis was not foreseen in the design of the study.

In view of the actual (nonsignificant) small differences in treatment effects, the probability that the unknown true treatment differences were < 10 points (which was considered to be the minimum relevant treatment effect) was estimated with Bayesian statistics. Using so-called noninformative a priori knowledge, this probability estimate is about 85%. Therefore, based on the results in 61 patients we cannot exclude the possibility of relevant treatment differences, but they seem unlikely.

The data in Table 1 show that randomization resulted in 3 comparable groups. There were no significant differences in age, sex, incidence of diabetes mellitus, arterial hypertension, coronary heart disease, atrial flutter, and peripheral atherosclerotic disease between the groups, and most importantly, the initial neurologic deficit expressed in the modified Mathew score was comparable in the 3 treatment groups.

Another question to be discussed is whether the dosage and volume of the agents and the duration of treatment were adequate. Most authors have given 10% glycerol or 10% dextran solution at 500 ml i.v. daily.\(^ {16-28}\) These preparations are well tolerated. But 10% glycerol 500 ml i.v. daily induced subclinical hemolysis in all but 1 of our patients. Possibly due to the initial injection of hapten, no allergic reactions to the dextran formulation (Rheomacrodex) were observed. The occurrence of consistent hemolysis and the 2 cases of left heart failure in this study contraindicate an increase in the concentration or volume load of the substances under investigation. Finally, as brain edema is most pronounced 2–5 days after acute occlusion of a cerebral artery, infusion treatment with glycerol and dextran over 7 days after acute stroke is reasonable.\(^ 3\) Similar regimens have been used in other trials.\(^ {16-23}\)

Although the physicians responsible for the patients were free to choose medication, there were no meaningful differences in the use of digitalis, diuretics, anticoagulants, and platelet antiaggregation drugs that could have influenced the recovery of neurologic function in the 3 treatment groups.

Deep vein thrombosis of the legs occurs in a high percent of patients with stroke.\(^ {33,24}\) In this study clinically apparent thrombosis, which clearly underestimates the true frequency, was significantly less frequently observed in the group that received dextran. During the first week of the trial no patient suffered from pulmonary embolism.

The presence of diabetes mellitus was randomized in this study since earlier reports had indicated that diabetic patients recovered less after stroke.\(^ {35}\) The 11 diabetic patients did not differ significantly in their neurologic score at Week 6 or at the following examinations when compared with all other patients. In addition there were no significant relations between neurologic recovery and the presence of concomitant diseases such as atrial flutter, arterial hypertension, etc. The lack of correlation could be due to the small number of subjects in each subgroup.

Table 3 describes the prospective controlled trials of glycerol or dextran in acute stroke that have been reported in the literature. All 4 authors who investigated dextran found the agent to be at least in part effective, but the findings should be interpreted with caution. Gilroy et al\(^ {22}\) followed their patients for only 10 days. In addition, their principal measure of outcome, the neurologic score, was not reported in adequate detail. Spudis et al\(^ {23}\) refrained altogether from statistical analysis of their results. Matthews et al\(^ {24}\) found dextran to

<table>
<thead>
<tr>
<th>Authors</th>
<th>Agent</th>
<th>Control</th>
<th>Number of patients*</th>
<th>Design</th>
<th>Delay†</th>
<th>Follow-up</th>
<th>Effectiveness of agent under study†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gilroy et al(^ {22})</td>
<td>D</td>
<td>PI</td>
<td>63/59</td>
<td>R</td>
<td>24–72</td>
<td>10 days</td>
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<tr>
<td>Spudis et al(^ {23})</td>
<td>D</td>
<td>S</td>
<td>30/29</td>
<td>R</td>
<td>24</td>
<td>21 days</td>
<td>(+)</td>
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<tr>
<td>Matthews et al(^ {24})</td>
<td>D</td>
<td>PI</td>
<td>52/48</td>
<td>R</td>
<td>?</td>
<td>6 months</td>
<td>(+)</td>
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<tr>
<td>Strand et al(^ {25})</td>
<td>D,P</td>
<td>S</td>
<td>52/50</td>
<td>R</td>
<td>48</td>
<td>28 days</td>
<td>+</td>
</tr>
<tr>
<td>Mathew et al(^ {16})</td>
<td>G</td>
<td>PI</td>
<td>25/29</td>
<td>R</td>
<td>72</td>
<td>14 days</td>
<td>+</td>
</tr>
<tr>
<td>Gelmers et al(^ {17})</td>
<td>G</td>
<td>S</td>
<td>50/50</td>
<td>R</td>
<td>12</td>
<td>28 days</td>
<td>0</td>
</tr>
<tr>
<td>Frithz and Werner(^ {18})</td>
<td>G</td>
<td>S</td>
<td>50/56</td>
<td>?</td>
<td>24</td>
<td>14 months</td>
<td>(+)</td>
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<tr>
<td>Gilsanz et al(^ {19})</td>
<td>G</td>
<td>PI</td>
<td>30/31</td>
<td>?</td>
<td>36</td>
<td>14 days</td>
<td>+</td>
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<tr>
<td>Larsson et al(^ {20})</td>
<td>G</td>
<td>PI</td>
<td>12/15</td>
<td>R</td>
<td>6</td>
<td>3 months</td>
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<tr>
<td>Friedli et al(^ {21})</td>
<td>G</td>
<td>PI</td>
<td>32/24</td>
<td>R</td>
<td>24</td>
<td>6 months</td>
<td>(+)</td>
</tr>
<tr>
<td>Frei et al</td>
<td>G,G + D</td>
<td>PI</td>
<td>18/23/20</td>
<td>R</td>
<td>24-32</td>
<td>6 months</td>
<td>0</td>
</tr>
</tbody>
</table>

D, dextran; PI, placebo; R, randomized; DB, double-blind; S, standard therapy; G, glycerol; P, phlebotomy.

* Number of patients in treatment/control group.
† Delay between onset of neurologic deficit and initiation of treatment, in hours.
‡ Effectiveness of agent under study: +, significant beneficial effect when compared with control; (+), beneficial effect only in a subgroup of patients with defined neurologic deficit; 0, no relevant beneficial effect.
be effective only in a retrospective analysis of a subgroup of patients with severe neurologic deficit. In the work of Strand et al.,\(^\text{16}\) again the principal measure of outcome, the neurologic score, was presented inadequately. The authors used dextran and phlebotomy simultaneously to achieve isovolumetric hemodilution; therefore the results of their study cannot readily be compared with the others.

Similar criticism holds for some of the trials in which the effect of glycerol has been studied. Mathew et al.\(^\text{18}\) found this agent to be beneficial in acute stroke, but followed the patient for only 14 days. In a well-designed and -evaluated study, Gelmers\(^\text{17}\) found no difference between glycerol and placebo. Fritz and Werner\(^\text{19}\) did not use random assignment to the different treatment regimens and found glycerol to be effective only in the subgroup of patients with intermediate neurologic deficit. Glycerol improved neurologic recovery in the trial by Gilsanz et al.,\(^\text{19}\) but the assignment to treatment or control group was again not at random, and the follow-up was only 14 days. Larsson et al.\(^\text{20}\) found no beneficial effect of glycerol, but they studied only 27 patients. Friedli et al.\(^\text{20}\) retrospectively divided their subjects into 3 groups according to the severity of initial neurologic deficit. Only those with intermediate impairment fared better with glycerol treatment.

Comparison of the different studies is also hampered by the variable delay between onset of stroke and onset of treatment. Furthermore, most authors did not include patients who had died during the trial in the statistical analysis of the principal measure of outcome. The studies therefore do not give information on an intention-to-treat basis.

In summary: There is no conclusive evidence for glycerol or dextran or the combination of both agents to be effective in acute stroke. Authors who have used steroids could not show consistent beneficial effects.\(^\text{21, 22}\) Recent reports about significantly better recovery after stroke under treatment with prostacyclin and calcium channel blockers and the findings of Strand et al., who used isovolumetric hemodilution, are encouraging.\(^\text{23, 24}\) The validity of these findings, however, must first be proven in larger prospective trials.

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References
41. Efron B: *The jackknife, the bootstrap and other resampling plans*. CBMS-NSF Regional Conference, series in applied mathematics, Philadelphia, 1982

**Key Words** • clinical trial • glycerol • dextran
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