Intravenous Glycerol in Cerebral Infarction: A Controlled 4-Month Trial

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SUMMARY  A double-blind, randomized trial was performed with 51 patients suffering from focal ischemic lesions in the territory of the middle cerebral artery. Intravenous infusions of 10% glycerol in 0.9% NaCl - 5% glucose solutions were administered twice daily for 6 days to 26 patients, and the same amount of NaCl - glucose solutions to 25 controls. Glycerol did not reduce mortality (9 deaths in each group). The functional recovery was assessed by repeated neurological examinations during the 4 month trial. Glycerol significantly improved global performances and motor and sensory functions in patients with moderate disability, but its effect on global performances was transient. The patients with severe disability were not improved at all.

BRAIN SWELLING and focal edema seem to play a major role during the acute phase of cerebral infarction. However, the beneficial effect of osmolar agents and corticosteroids has been questioned. Intravenous glycerol can reduce cerebral edema, but it has been claimed that other effects on cerebral metabolism may be beneficial. Three clinical trials have shown some improvement in patients treated with intravenous glycerol, while a fourth did not confirm these results. We report results obtained in elderly patients who received either glycerol, or a placebo, shortly after the onset of a focal ischemic lesion localized in the territory of the middle cerebral artery.

Selection of Patients and Methods

Sixty-four patients admitted to the Department of Medicine at our hospital were selected within 48 hours following the onset of an ischemic cerebral infarction. An informed consent could not be obtained since most patients had impairment of consciousness. They were selected by 2 physicians, 1 of the authors and an independent supervisor. This procedure was accepted by the ethical committee of the Department. Physical examination showed a neurological deficit whose manifestations were typical for a focal lesion in the territory of the middle cerebral artery. In all patients the cerebrospinal fluid was bloodless. This diagnosis was confirmed by EEG and isotopic gamma encephalography. Cerebral arteriography was performed only if a surgical procedure had to be considered (6 patients). We excluded those patients who had obvious signs or clinical suspicion of intracranial hemorrhage, transient ischemic attacks, lacunar stroke, cerebral tumor, as well as severe heart failure, shock, generalized neoplasia and history of severe mental disorders.

The patients who met our criteria were divided into 2 groups by means of a table of random numbers. One group received 25 g of glycerol intravenously twice daily for 6 days, and the other received the same amount of fluid without glycerol. Intravenous infusions were administered from 8 to 10 a.m. and from 4 to 6 p.m. The hospital pharmacist prepared 12 bottles containing 250 ml of a solution of NaCl 0.9% (1/3) and glucose 5% (2/3) with or without glycerol for each patient. The bottles were coded and identical bottles containing 250 ml of a solution of NaCl 0.9% (1/3) and glucose 5% (2/3) without glycerol were prepared. Anticoagulants and drugs reducing platelet aggregation were administered in patients who had probable embolism, in which some recovery could be expected, and, therefore, where a prevention was still worthwhile. Any change in nursing or the rehabilitation program was avoided during the study.

A neurological examination was performed by the same investigator (R.F.) on day 0, 1, 2 and 7 (infusion period), at the end of weeks 2, 3 and 4 and on the 2nd, 3rd and 4th month (follow-up period). The severity of the neurological deficit was assessed by a scoring system in which the lower the score the more severe the functional disability. 1. Signs of intracranial hypertension (max: 24 points): alertness (8), orientation (6), ventilation (6), pupils (4). 2. Cortical functions (73): aphasia (25), alexia (12), agrapnia (6), acaulcia (6), ideational apraxia (6), constructional apraxia (6), agnosia (4), right-left confusion (4). 3. Motor functions (32): conjugated eye deviation (6), face (6), arms (10), legs (10). 4. Sensory functions (26): face (6), arms (10), legs (10). 5. Global performances (46): walking (25), eating (5), washing and dressing (6), sphincter control (10). 6. Others (14): reflexes (8), visual field (6). The lower the level of consciousness the lower the total score, as alertness is part of cortical, but also of most other individual functions. The scores on day 0 and their changes during the infusion and the follow up periods in the placebo and the glycerol group were compared by means of a non-parametric test (Wilcoxon-White 2-sample rank test).

The following determinations were made during the infusion period: 24-hour urinary volume, blood pressure and pulse rate before and after each infusion, screening test for hematuria (Haemastix®) twice daily (if positive a blood sample was drawn for determination of plasma hemoglobin).
TABLE 1  Distribution of Patients in Glycerol and Control Group

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Placebo group</th>
<th>Glycerol group</th>
</tr>
</thead>
<tbody>
<tr>
<td>— selected on admission</td>
<td>32</td>
<td>32</td>
</tr>
<tr>
<td>— excluded during the 1st week</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>— included in the study</td>
<td>25</td>
<td>26</td>
</tr>
<tr>
<td>— male/female</td>
<td>11/14</td>
<td>15/11</td>
</tr>
<tr>
<td>— with left-/right-sided lesion</td>
<td>17/8</td>
<td>12/14</td>
</tr>
<tr>
<td>— on heparin, acenocoumarol</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>— on aspirin, dipyridamole</td>
<td>15</td>
<td>11</td>
</tr>
</tbody>
</table>

| Mean age ± SEM | 72 ± 2 | 70 ± 2 |
| Mean initial score ± SEM | 92 ± 11 | 100 ± 9 |
| Mean time from onset of stroke to 1st infusion (hour ± SEM) | 16 ± 2 | 19 ± 2 |

Results

Thirteen of the 64 patients selected on admission to the hospital were excluded during the first week of the study; 9 of them in which the initial clinical neurological diagnosis was not confirmed, 2 for neoplasia, 1 for receiving corticosteroids and 1 for sudden worsening of the cerebral condition on day 0 (table 1). This left 51 patients who were divided into 2 groups which were roughly equivalent in regard to most criteria. There was only a difference in the proportion of left- and right-sided lesions but the total scores in the 2 groups on day 0 did not differ significantly. The delay between the onset of the stroke and the infusions ranged in the glycerol group between 1-6 hours (9 cases), 7-12 (1), 13-24 (10), and 25-48 (6), but it did not differ significantly from that of the placebo group.

Mortality

The overall death rate during the 4 months was high (35%), as could be expected in such elderly patients. Glycerol infusions did not reduce the mortality (9 deaths in each group). The death rate of patients with a severe neurological deficit was much higher than that of patients with a moderate deficit, and it was independent of whether they had received glycerol infusions or not (fig. 1). Of the 18 deaths, 1 was directly related to the cerebral infarction (6 in the placebo and 5 in the glycerol group), 6 were due to pulmonary embolism and/or myocardial infarction (3 in each group) and 1 was due to a gastrointestinal hemorrhage (this patient was not on anticoagulants).

Functional Recovery

Functional recovery was assessed by changes of scores during the infusion and the follow up period. The changes of total scores determined in each patient of the control and the glycerol group did not show any obvious difference; there was only a slight difference in favor of glycerol on day 2 (∗∗∗p < 0.05). Since the initial scores varied largely from subject to subject 2 separate analyses of the scores were done: 1 in patients with a moderate neurological deficit (initial score ≥100) and the other in those who had a severe deficit (initial score <100). As shown in figure 1 the patients with a moderate deficit were improved by glycerol, whereas those with a severe deficit were not improved at all. In the former, the effect of glycerol on the total scores was significant but transient, that is, from day 1 to day 21 only. The scores of patients with a moderate deficit were analyzed in more detail (table 2). Glycerol appeared to be most effective on global performances, i.e. walking, eating, washing and dressing and sphincter control, but the differences between controls and patients on glycerol were significant only from day 3 to 7 (infusion period). The beneficial effect of glycerol on motor and sensory functions was less marked, but the differences of the scores were still significant during the follow up period (day 7 to 60 and day 7 to 120 for the motor and sensory functions respectively). Other functions were not improved by glycerol: cortical functions, i.e. aphasia, and the signs related to intracranial hypertension, i.e. alertness, ventilation.

Untoward Effects

Diuresis during the infusion period was unchanged. The systolic blood pressure increased slightly (mean + 5 mm Hg) during the 2-hour period of glycerol infusion but it did not change in the controls. Diastolic blood pressure and pulse rate were unchanged in the 2 groups. Screening tests for hematuria were positive 5 times but all these patients had an indwelling catheter and plasma hemoglobin concen-
The results indicate that glycerol infusions improve during the follow-up period (day 7 to 60 and day 7 to 7) and motor and sensory functions were improved washing, etc.), which are essential for the patient's care, were improved during the infusion period (day 3 to 7) and motor and sensory functions were improved during the follow-up period (day 7 to 60 and day 7 to 120 respectively). Hence, glycerol does seem to have a beneficial effect mainly in the early phase of the rehabilitation program.

As pointed out by Larsson et al., the design of clinical trials in patients with early stroke is very difficult. Analysis of the results of the present study needs some comment. Firstly, in the placebo group there were more patients with left-sided lesion than in the glycerol group (table 1). This might have played a role in the evaluation of the cortical functions, but there is no evidence that this influenced the other functions which were improved by glycerol (table 2). Secondly, the mortality of patients with a severe neurological deficit was high. The changes in their scores seemed to indicate a definite improvement throughout the period of the study (fig. 1). However, these scores only reflect the functional recovery of the patients until their deaths. Patients with severe deficit and alive at the end of the study did not seem to be improved by glycerol, but their number was too small to draw any conclusion. In patients with a moderate deficit the mortality was lower. Hence we were able to perform another analysis including only the scores of patients alive at the end of the study. The differences between scores under placebo and glycerol were again significant. Thirdly, most patients received anti-coagulants or agents which reduce platelet aggregation; hence it was impossible to analyze the data after exclusion of these patients. It can only be said that these patients were evenly distributed in the control and the glycerol groups.

### Discussion

The patients included in this study were carefully selected and followed for 4 months. All those who did not have obvious signs of a focal ischemic lesion in the territory of the middle cerebral artery were excluded. The results indicate that glycerol infusions improve the functional recovery of patients with a moderate neurological deficit. Global performances (eating, washing, etc.), which are essential for the patient's care, were improved during the infusion period (day 3 to 7) and motor and sensory functions were improved during the follow-up period (day 7 to 60 and day 7 to 120 respectively). Hence, glycerol does seem to have a beneficial effect mainly in the early phase of the rehabilitation program.

### Acknowledgment

We would like to thank the staff of the Department of Neurology for their helpful advice and assistance. This study was supported by a grant from the Merrell International Research Center, Strasbourg.

### References

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Stroke. 1978;9:484-486
doi: 10.1161/01.STR.9.5.484

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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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