Treatment of Acute Cerebral Hemorrhage
With Intravenous Glycerol
A Double-Blind, Placebo-Controlled, Randomized Trial

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Background and Purpose: Hitherto, treatment of acute cerebral hemorrhage with intravenous glycerol has not been evaluated in rigorous clinical studies with sufficient patient numbers.

Methods: We undertook a double-blind, stratified and randomized, placebo-controlled clinical trial. Only patients with a first stroke admitted to the hospital within 24 hours after onset of symptoms were recruited, provided computed tomography confirmed hemorrhage and informed consent was obtained. After stratification into alert, semicoma, and coma subgroups using the Glasgow Coma Scale, 107 patients received active treatment (500 ml of 10% glycerol in saline by intravenous infusion over 4 hours on 6 consecutive days) and 109 were given corresponding saline treatment. Using a variety of objective scoring systems, patients were followed up for up to 6 months.

Results: At follow-up, all measures of outcome in the treated and control groups were very similar. At 6 months, respective mortality rates were 37 of 107 and 33 of 109. Corresponding mean±SD improvements in Scandinavian Stroke Study Group scores were 8.35±16.9 versus 11.55±15.6 (long-term) and 0.64±7.3 versus 2.40±6.9 (prognostic), and improvements in the Barthel Index ratings were 10.72±24.7 versus 13.95±23.3, respectively. Glasgow Coma Scale score improvements in the survivors were 0.81±1.5 and 1.16±1.7 in the treated and control groups, respectively. Hemolysis (generally subclinical) was the only adverse effect of glycerol noted.

Conclusions: In the absence of any clinically or statistically significant difference in outcome between the treated and control groups, this trial provides no justification for glycerol therapy following acute cerebral hemorrhage.

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KEY WORDS • cerebral hemorrhage • clinical trials • glycerin

Acute spontaneous supratentorial intracerebral hemorrhage (SSIH) has considerable mortality and morbidity, and it is believed that edema around the hemorrhagic lesion contributes to early death from transtentorial herniation.1-3 In an attempt to reduce the damaging effects of cerebral edema, various forms of treatment (in particular, steroids and hyperosmolar agents) have been advocated in the past. However, clinical trials now indicate that steroid treatment has no place in the management of acute hemorrhagic stroke.4,5

It is possible that glycerol may have a beneficial effect in cerebral hemorrhage. In experimental animals with cerebral hemorrhage, glycerol reduces cerebral edema without rebound upon withdrawal6 and normalizes increased vascular tone.7 In an open clinical trial on SSIH patients,8 glycerol was shown to increase cerebral perfusion through hemodilution and reduction of raised intracranial pressure. Moreover, clinicians have often used glycerol empirically in cerebral hemorrhage, even though hitherto there have been no adequate controlled trials to evaluate its possible benefits.

The current double-blind, placebo-controlled, randomized trial was undertaken to determine whether treatment of acute SSIH with intravenous glycerol has a clinically significant favorable influence on mortality and morbidity over the ensuing 6 months.

Subjects and Methods

Case Selection

Consecutive patients aged 30–80 years with no history of stroke were entered into the study if SSIH was confirmed on computed tomography (CT). Informed consent was obtained from the patients or their close relatives. The exclusion criteria were posterior fossa hemorrhage, hemorrhage resulting from aneurysm or arteriovenous malformation, any other condition warranting neurosurgery, or concomitant medical problems including collagen-vascular disease, bleeding diathesis, and anticoagulant therapy. Patients commencing trial medication were to have it withdrawn if they required...
neurosurgical treatment or if it was deemed necessary by the attending neurologist. However, outcome and neurological scores were assessed in all patients because analysis was on an intention-to-treat basis.

Methods and Analysis

Clinical method. History and physical findings, including detailed neurological assessment, were recorded on admission. In particular, the time from onset of symptoms to admission, history of hypertension, vascular disease, cardiac arrhythmia, diabetes mellitus, smoking, drug treatment, and relevant family history were noted. At each examination, neurological variables were documented without knowledge of the treatment administered. The scoring system of the Scandinavian Stroke Study Group (SSScand) and score on the Glasgow Coma Scale (GCS) were used to assess patients on admission; before treatment (on the first day they received trial medication) and on days 3, 7, 14, 21, and 28; and then monthly for 5 months. One month after entering the trial and at monthly intervals thereafter, the overall score for activities of daily living was assessed using the Barthel Index. The cause of death (brain herniation, pneumonia, sepsis, airway obstruction, recurrent stroke, and others) was ascertained as far as possible.

Laboratory parameters. The following were checked at the initial examination: complete blood count (hemoglobin concentration, packed cell volume, and white cell, platelet, and reticulocyte counts), plasma glucose, serum biochemical indexes, and electrocardiogram. The complete blood count and serum biochemical indexes were repeated on day 7.

Computed tomographic method. SSIH was confirmed by noncontrast brain CT using the GE 9800 system with standard window settings and 10-mm slices from the orbitomeatal line to the vertex. CT was performed as soon as possible and not later than 24 hours following admission and was repeated between days 7 and 10 and whenever warranted by the patient's clinical condition. The size of the lesion (volume of hemorrhage with and without edema) was measured by computer at the physician's diagnostic console.

Other investigations. Cerebral angiography was performed in patients in whom an aneurysm or arteriovenous malformation was suspected and in patients with unusual sites of bleeding.

Treatment. Due to differing prognoses depending on the initial severity of the stroke, patients were stratified according to the pretreatment GCS score: coma (score of 3–7), semicoma (score of 8–11), and alert (score of 12–15). Active treatment was 500 ml of 10% glycerol (generic) in physiological saline, and placebo was 500 ml of physiological saline. Each treatment was administered intravenously over 4 hours for 6 consecutive days.

Design and analysis. Based on previous statistics, 12,13 240 patients were expected to enter the trial over 24 months. A group sequential approach was adopted, and treatment was allocated according to a stratified randomized block design. Differences from pretreatment values (for GCS score, prognostic and long-term items on SSSScand) or initial findings (score on Barthel Index) were expressed as δ scores and used as measures of outcome. See Appendix for definition of symbols.

### TABLE 1. Clinical Profile of All Patients at Entry

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Glycerol (n=107)</th>
<th>Placebo (n=109)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male/female)</td>
<td>Alert 55/17 49/24</td>
<td>Semicoma 7/8 8/7</td>
</tr>
<tr>
<td>Age (mean±SD yrs)</td>
<td>Coma 10/10 9/12</td>
<td>Time to treatment* (mean±SD hrs) 29±16 28±11</td>
</tr>
<tr>
<td>Ischemic heart disease†</td>
<td>Hypertension 64 58</td>
<td>Diabetes mellitus 7 7</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Smokers and ex-smokers 28 37</td>
<td></td>
</tr>
<tr>
<td>Volume of SSIH (mean±SD ml)</td>
<td>28.5±29.0 32.3±30.5</td>
<td></td>
</tr>
<tr>
<td>Volume of SSIH+edema (mean±SD ml)</td>
<td>52.9±53.3 69.0±78.1</td>
<td></td>
</tr>
<tr>
<td>Computed tomographic localization of SSIH</td>
<td>Midline/bilateral 3 1</td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>Left 51 55</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Right 53 53</td>
<td></td>
</tr>
</tbody>
</table>

SSIH, spontaneous supratentorial intracerebral hemorrhage. One in each group had atrial fibrillation. With respect to these characteristics, there were no clinically important or statistically significant differences (using χ² or t tests as appropriate) between groups.

Analyses were performed on all patients (scoring death as 0 on the clinical scales) and on survivors only. A subsidiary analysis was undertaken on the alert subgroup. Patients whose trial medication was stopped when gross hemolysis was suspected were also followed up and included in the analyses on an intention-to-treat basis.

The 1-month long-term δ score was selected as the monitoring variable. One interim analysis was planned after the entry of 120 patients, using the latter variable and an overall significance level of 5% for any difference (Δ) in the mean δ scores. Assuming that the δ scores follow a normal distribution across strata within each treatment group, the power is 0.95 at an absolute value of Δ of ½σ, where σ is the (common) SD of the δ scores. In practice ½σ is about 5–7, and this range was taken as the measure of clinical significance. Parametric and nonparametric methods were employed for the interim and final analyses. Follow-up analyses of corresponding variables were performed on the respective δ scores at 2, 3, 4, 5, and 6 months, results at 6 months being taken as the clinically definitive assessment. The SAS package was used for the analyses. For ethical reasons, the trial was also subjected to continuous informal monitoring of death rate and side effects (hemolysis).

Results

After 120 patients were recruited, the interim analysis did not reveal a significant result. The trial was then continued on its second phase but was not run to final completion because the probability that Δ was >5 for the long-term δ scores had become negligible based on a Bayes posterior normal distribution calculation (see Appendix and Table 4). Patients randomized to the two
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reasons.

withdrawn when gross hemoglobinuria was suspected.

was referred for neurosurgery after randomization.

is a summary of the predictive analysis based on the

neurological and rehabilitation scores at 6 months are summarized in Table 3. Table 4

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long-term scores. The analysis shows that, using this regimen of glycerol therapy, no clinically or

outcome) could be expected.

Hemolysis (usually subclinical) was the only drug side
effect observed. Table 2 shows the respective numbers of patients in whom placebo or glycerol treatment was
withdrawn when gross hemoglobinuria was suspected. Table 5 summarizes pertinent hematologic findings for
all 216 patients entering the trial. For patients surviving for up to 7 days, the mean reductions from pretreatment
hemoglobin values were 0.54 and 0.12 g/dl following
treatment with glycerol and placebo, respectively. Thus,
either the absolute nor the relative changes in hemo-
globin concentration could be regarded as clinically
significant.16

Discussion

Hitherto, studies purporting to evaluate the possible
beneficial effect of intravenous glycerol in patients with
acute stroke have yielded contradictory and inconclu-
sive results.17-25 Commonly, there was no attempt to
distinguish hemorrhagic from ischemic episodes (espe-
cially in earlier trials), and if attempted, objective
confirmation of the diagnosis with CT was lacking or
inconsistent.17-24 The study by Frei et al,25 in which
pretreatment CT was performed on all patients, con-
cerned ischemic stroke. Other important shortcomings
in the design and execution of these investigations
included failure to stratify patients according to stroke
severity (anticipated prognosis), prolonged delays be-
fore initiating treatment, limited measures of outcome,
exclusion of the most severely affected patients, too few
patients, and insufficient period of follow-up.

By contrast, our trial entailed CT confirmation of
SSIH, inclusion of both mild and severe cases, corre-
spanding stratification based on level of consciousness
(GCS score), and inclusion of only patients with onset of
symptoms in the 24 hours before admission. In the final

treatment groups (216 in all) were comparable with
respect to age, sex distribution, and prior clinical features
(Table 1) and were recruited over 31 months. No patient
was referred for neurosurgery after randomization.

Table 2 summarizes the status of all patients 6 months
after SSIH, with respect to survival, deaths, and loss to
follow-up. For all accountable trial patients treated with
glycerol or placebo, the neurological and rehabilitation
scores (outcome) could be expected.

Alert patients

Semicoma

Coma

Placebo

Glycerol

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spanding stratification based on level of consciousness
(GCS score), and inclusion of only patients with onset of
symptoms in the 24 hours before admission. In the final

Table 2. Status of All Trial Patients 6 Months After Spontaneous Supratentorial Intracerebral Hemorrhage

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Entered</th>
<th>Surviving</th>
<th>Dead</th>
<th>Lost to follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>109</td>
<td>67 (1)</td>
<td>33 (1)</td>
<td>9</td>
</tr>
<tr>
<td>Glycerol</td>
<td>107</td>
<td>60 (7)</td>
<td>37 (2)</td>
<td>10</td>
</tr>
<tr>
<td>Alert</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>73</td>
<td>57 (1)</td>
<td>8 (1)</td>
<td>8</td>
</tr>
<tr>
<td>Glycerol</td>
<td>72</td>
<td>52 (7)</td>
<td>14 (2)</td>
<td>6</td>
</tr>
<tr>
<td>Semicoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>15</td>
<td>8</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Glycerol</td>
<td>15</td>
<td>8</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Coma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>21</td>
<td>2</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>Glycerol</td>
<td>20</td>
<td>0</td>
<td>19</td>
<td>1</td>
</tr>
</tbody>
</table>

Values are number of patients. In glycerol group death was attributed to brain stem herniation in 27 patients (only six of whom were alert at entry), pneumonia in two, septicemia in one, myocardial infarction in two, and unknown or other causes in five. Corresponding figures for placebo group were 20 (three alert at entry), four, three, and three. Numbers in parentheses refer to patients who developed gross hemoglobinuria, warranting discontinuation of trial medication.

Table 3. Neurological and Rehabilitation Score Changes at 6 Months

<table>
<thead>
<tr>
<th>Score</th>
<th>All accountable patients</th>
<th>Survivors followed up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>Glycerol</td>
<td>Placebo</td>
</tr>
<tr>
<td>n</td>
<td>Mean±SD</td>
<td>n</td>
</tr>
<tr>
<td>Long-term</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>100</td>
<td>11.55±15.6</td>
</tr>
<tr>
<td>Alert patients</td>
<td>65</td>
<td>13.86±14.89</td>
</tr>
<tr>
<td>Prognostic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>100</td>
<td>2.40±6.9</td>
</tr>
<tr>
<td>Alert patients</td>
<td>65</td>
<td>3.68±6.7</td>
</tr>
<tr>
<td>Glasgow Coma Scale</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>100</td>
<td>-1.77±5.0</td>
</tr>
<tr>
<td>Alert patients</td>
<td>65</td>
<td>-1.06±4.8</td>
</tr>
<tr>
<td>Barthel Index</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>96*</td>
<td>13.95±23.3</td>
</tr>
<tr>
<td>Alert patients</td>
<td>62*</td>
<td>17.50±25.8</td>
</tr>
</tbody>
</table>

*Though 6-month follow-up scores were available, a few patients did not have initial (1-month) Barthel Index score for a variety of logistic reasons.
analysis data were available for 216 patients, nearly the same number as had been projected, and those assigned to glycerol and placebo treatment had very similar pretreatment clinical profiles (Table 1). Furthermore, our measures of outcome included the death rate, a series of formal neurological deficit scores, and objective evaluation of rehabilitation status, all followed up for 6 months.

The only important adverse effect of treatment we encountered was intravascular hemolysis. A critical study of the extent to which it affected patients entering our trial and the likely mechanism were reported elsewhere. The latter in vivo and in vitro investigation revealed that hemolysis probably resulted from glycerol at the site of infusion rapidly entering erythrocytes and destroying them in more central veins due to osmotically induced swelling beyond a critical limit. Thus, so long as the infusion rate did not exceed 125 ml/hr (even temporarily), clinically significant hemolysis did not ensue. The use of glycerol solutions containing small amounts of fructose may also overcome hemolysis to some extent, there being in vitro evidence that osmotic fragility can be mitigated by this means. 26 Japanese clinicians have reported by Frei et al. 25 Indeed, following 6 days of therapy.

Regarding conventional regimens of intravenous glycerol, our relatively large trial in patients with all grades of acute SSIH provides no evidence in support of such therapy.

### Appendix

#### Definition of δ Score

For individual \( i \) in group \( i (i=1 \text{for glycerol}, i=2 \text{for placebo}) \) define \( \delta_i \) as (score at month \( k) - \text{(pretreatment score)} \). Therefore, \( \bar{\delta} = \sum_i \delta_i / n \), estimates the mean change \( \Delta \) in group \( i \), and \( \bar{\delta} = \bar{\delta}_1 - \bar{\delta}_2 \) estimates the mean difference \( \Delta = \Delta_1 - \Delta_2 \) between groups.

#### Bayes Posterior Density Calculations

The \( \delta \) scores here are based on the 6-month long-term scores in Table 4. The pooled variance estimator for the variance \( \sigma^2 \) of the \( \delta \) scores is given by

\[
s^2 = \frac{2n}{\sum_i \sum_j (\delta_{ij} - \bar{\delta})^2} / (n_1 + n_2 - 2)
\]

The posterior density for \( \bar{\delta} \) is taken as normal with mean \( \bar{\delta} \) and variance \( s^2 / (n_1 + n_2) \). Then, for example

### Table 4. Probability Calculations for Difference in Pretreatment and 6-Month Mean Long-Term Scores Between Patients Receiving Placebo and Glycerol

<table>
<thead>
<tr>
<th>Group</th>
<th>Placebo</th>
<th>Glycerol</th>
<th>( \bar{\delta} ) (mean±SEM)</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>100</td>
<td>97</td>
<td>-3.2±2.32</td>
<td>0.95</td>
</tr>
<tr>
<td>Alert patients</td>
<td>65</td>
<td>66</td>
<td>-3.68±2.93</td>
<td>0.67</td>
</tr>
<tr>
<td>Alert survivors</td>
<td>67</td>
<td>60</td>
<td>-1.92±1.99</td>
<td>0.94</td>
</tr>
<tr>
<td>Alert survivors</td>
<td>57</td>
<td>52</td>
<td>-0.66±1.98</td>
<td>0.98</td>
</tr>
</tbody>
</table>

\( \bar{\delta} \), mean difference in score change between groups.

*Corresponding value for 1-month scores was 0.0002.

### Table 5. Hemoglobin Values at Entry and at 1 Week

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Day 1</th>
<th>Day 7</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( n )</td>
<td>Mean±SD</td>
<td>( n )</td>
</tr>
<tr>
<td>All patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>109</td>
<td>13.65±1.77</td>
<td>86</td>
</tr>
<tr>
<td>Glycerol</td>
<td>107</td>
<td>13.83±1.73</td>
<td>79</td>
</tr>
<tr>
<td>Alert patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>73</td>
<td>13.80±1.78</td>
<td>64</td>
</tr>
<tr>
<td>Glycerol</td>
<td>72</td>
<td>13.80±1.83</td>
<td>63</td>
</tr>
</tbody>
</table>

Values are g/dl.
*Statistically significant difference from 0 and from value in placebo group (p<0.002; 95% confidence interval -0.82 to -0.26 g/dl). Among individual patients in placebo and glycerol groups, largest hemoglobin reductions were 2.6 and 3.1 g/dl, respectively.
\[ p(\Delta ; x) = 1 - \Phi \left( \frac{x - \Delta}{\Delta} \right) \]

where \( \Phi(z) = \int_{-\infty}^{z} \frac{1}{\sqrt{2\pi}} e^{-t^2/2} dt \) is the standard normal cumulative distribution function.

Acknowledgments

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Treatment of acute cerebral hemorrhage with intravenous glycerol. A double-blind, placebo-controlled, randomized trial.
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