Intravenous Fluosol in the Treatment of Acute Myocardial Infarction

Results of the Thrombolysis and Angioplasty in Myocardial Infarction 9 Trial

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Background This study was performed to determine the safety and potential efficacy of an intravenous perfluorochemical emulsion (Fluosol) as an adjunct reperfusion therapy aimed at preventing reperfusion injury for patients with acute myocardial infarction.

Methods and Results Patients (430) were randomized in a prospective open-labeled study, 213 to receive Fluosol and 217 to receive no Fluosol, along with 100 mg of tissue-type plasminogen activator given over 3 hours. Major end points included global ejection fraction, regional wall motion analysis, infarct size as measured by tomographic thallium imaging, and a composite clinical outcome measure. Baseline patient and angiographic characteristics were similar in the two groups. No significant difference in global ejection fraction (52% without Fluosol, 51% with Fluosol) or regional wall motion (−2.4 SD/chord with Fluosol, −2.2 SD/chord without Fluosol) was demonstrated in patients receiving Fluosol versus those not receiving Fluosol, nor was there a significant difference in thallium infarct size. Although Fluosol-treated patients with anterior infarction had an insignificantly lower mean infarct size (18.7% of the left ventricle) compared with patients with anterior infarction not treated with Fluosol (21.2% of left ventricle), this trend was not evident in the median infarct size values (22% versus 17%), left ventricular ejection fraction values (46% without Fluosol, 47% with Fluosol), or regional wall motion (−2.5 SD/chord in both groups). Rates of death and stroke were no different in the two groups; however, patients who received Fluosol experienced less recurrent ischemia. Patients receiving intravenous Fluosol had more transient congestive heart failure and pulmonary edema, perhaps because of necessary fluid administration. There was no difference in hemorrhagic complications between the two study groups.

Conclusions When given with a thrombolytic agent, Fluosol was associated with improvement in ventricular systolic function, reduction in thallium infarct size, or overall clinical outcome. Fluosol was, however, associated with a reduction in ischemic complications and with an increase in pulmonary edema and congestive heart failure. (Circulation. 1994;90:114-120.)

Key Words • myocardial infarction • ventricles • Fluosol • radioisotopes

The amount of myocardial damage is the primary determinant of survival and functional status after acute myocardial infarction (MI). Although reperfusion reduces infarct size, improves systolic left ventricular (LV) function, leads to lower ventricular volumes, reduces symptomatic congestive heart failure, and improves mortality, the magnitude of this effect has been less substantial than initially hoped. Efforts to improve the amount of myocardial salvage have focused on earlier reperfusion, more complete perfusion, and prevention of infarct vessel reocclusion.

Another approach to improving reperfusion therapy arose from animal studies indicating that the amount of myocardial salvage after reperfusion may be limited by anatomic and metabolic consequences of reperfusion. This phenomenon, referred to as reperfusion injury, has been limited in animal models by Fluosol, a perfluorochemical emulsion. These studies have reported that the intracoronary administration of oxygenated Fluosol resulted in smaller infarct size and improved systolic LV function. Supportive evidence of beneficial effects, in terms of both preservation of the microvasculature and more substantial salvage of myocardium, has been developed. In one study of 26 patients, the intracoronary administration of Fluosol in the setting of direct angioplasty for anterior MI produced a marked improvement in global and regional LV function assessed by contrast ventriculography and a reduction in tomographic thallium-estimated infarct size. Mechanisms that have been raised as the pathophysiological basis for reperfusion injury include leukocyte release of free radicals and other toxic metabolites at the time of reperfusion and destruction of microvasculature. Fluosol has been demonstrated to be a potent inhibitor of white cell chemotaxis and activation.
The Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) 9 study was designed to determine whether intravenous Fluosol in conjunction with thrombolytic therapy would reduce myocardial infarct size as estimated by thallium scintigraphy or improve systolic LV function and provide preliminary evidence of clinical effect.

Methods

Patient Enrollment

Ten university and large cardiac referral centers participated in this trial (see “Acknowledgments”). The protocol was approved by the institutional review board at all participating sites. Patients were identified and enrolled in the study in the emergency room setting. Inclusion criteria included symptoms consistent with an acute MI of <6 hours’ duration unresponsive to sublingual nitroglycerin; age >18 and <75 years of age; ST-segment elevation of at least 0.1 mV in at least two of six precordial leads, two of three inferior leads, or in both leads I and aVL; and ability and willingness to give informed consent to participate in this study. Exclusion criteria included treatment with Fluosol within the previous 6 months, ongoing renal dialysis, clinically significant liver disease, chronic obstructive pulmonary disease, other serious advanced illnesses likely to limit life expectancy, prolonged cardiopulmonary resuscitation (>7 minutes) within the previous 2 weeks, other standard contraindications to thrombolytic therapy, previous coronary artery bypass graft surgery, previous Q-wave infarction, and cardiogenic shock.

Treatment

Once inclusion and exclusion criteria were met, patients were randomized by telephone by the Coordinating Center at Duke University Medical Center. All patients were initially treated with 324 mg of chewable aspirin, intravenous heparin, and 100 mg of intravenous tissue-type plasminogen activator (TPA) over 3 hours. In addition, patients received intravenous atenolol unless they had atrioventricular block, systolic blood pressure <100 mm Hg, heart rate <60 beats per minute, bibasilar rales, or a significant history of bronchoespasm. Intravenous morphine, nitroglycerin, and atropine also were used at the discretion of the investigator.

After the initiation of the above therapy, patients were randomized to receive intravenous Fluosol or no Fluosol. Because of previous concern with hypotension in canine studies, intravenous Fluosol was administered at the rate of 1 mL/min for the first 5 minutes, 5 mL/min for the next 5 minutes, and 20 mL/min until a total of 15 mL/kg had been administered. The dose was reduced in the presence of any sign of pulmonary congestion or edema; 77% of patients received the full dose. All patients continued to receive intravenous heparin at a rate of 1000 U/h to maintain the partial thromboplastin time at 1.5 to 2 times the control value. An attempt was made to administer oxygen at 100% concentration (6 to 10 L/min) for 8 hours after randomization to maximize the oxygen carried by the study agent; this goal was achieved in 89% of Fluosol-treated patients and in 86% of control patients.

Cardiac Catheterization

An effort was made to perform cardiac catheterization, including coronary angiography and left ventriculography, 5 to 14 days after the administration of thrombolytic therapy. Left ventriculograms of adequate quality were obtained within the prespecified 5- to 14-day window in 312 (73%) of the patients enrolled in the trial. An additional 32 left ventriculograms were obtained before 5 days because of recurrent ischemia, and 6 studies were completed after 14 days, giving a total of 81% of randomized patients with studies suitable for analysis. Of the remaining patients, 34 studies were done but were of inadequate quality, 18 were not done because the patients died, 8 were medically contraindicated, 8 were not obtained due to patient preference, and 12 were not obtained for other reasons. All cineangiograms were evaluated independently at the core angiographic laboratory at the Cleveland Clinic. Quantitative analysis included TIMI perfusion grade, visual percent stenosis of the infarct-related artery, and global LV function as determined by the area-length method, which was expressed as global ejection fraction. Regional wall motion of the infarct and noninfarct zones was evaluated quantitatively and expressed as SD/chord using the centerline chord method. Technically inadequate studies due to inadequate contrast or frequent ventricular extrasystoles were not included in the analysis. All efficacy analyses were performed twice: in the primary analysis, only patients with studies within the 5- to 14-day window were used; then an analysis was done using all patients with technically adequate studies. Since the treatment comparisons did not differ with either analysis strategy, only the results for the analysis of 5- to 14-day studies are presented.

Thallium Scintigraphy

Infarct size was also measured by tomographic thallium imaging 5 to 14 days after thrombolytic therapy. All thallium scans were evaluated independently at the core nuclear laboratory at the University of Michigan. An effort was made to exercise all patients using the standard Bruce protocol to a symptom-limited end point unless the patient was incapable, in which case pharmacological stress with diprydamole or adenosine was used. An injection of 3 mCi IV of 201TI was given at peak exercise or after pharmacological stress. After the injection, exercise was maintained for at least 60 seconds. Imaging was started 15 minutes after cessation of exercise. Three to 5 hours after exercise, the resting image was acquired after injection of an additional 1 mCi of 201TI. In both cases, 32 images were acquired on an 84x84 matrix, with care taken to minimize motion artifact.

After the images were translated into digital images, they were stored on floppy disk and sent to the Thallium Core Laboratory. Because the data were collected on multiple-imaging systems, a Siemens Microdelta computer and software developed by Sudbury Inc were used to convert the data into one format. Care was taken to label the disks so that the treatment assignment of the patient was unknown during the processing and analysis of the data.

A tomographic image was analyzed using the “bull’s-eye” approach, in which peak 201TI activity was profiled along 60 radii extending from the center of the left ventricle. A polar map of the left ventricle then was constructed using the histograms of cross-sectional and sagittal images. Relative tracer distribution was color coded to provide normalized ratios compared with maximal activity and with a database of age-matched normal subjects. After the polar map was divided into typical vascular territories defined from a database of patients with single-vessel disease, the estimate of infarct size was made based on the percentage of vascular territories of the left ventricle with regional activity below 2.5 SD of normal.

Resting tomographic thallium studies were technically adequate and within the 5- to 14-day window in 258 patients (60%). An additional 67 studies were done outside the 5- to 14-day window, for a total of 325 technically adequate studies (76%). Of the remaining patients, 17 studies were not done because the patients died, 16 were technically inadequate, 10 were done with planar images only, 6 could not be done because of the patient's weight, 6 were not done because of medical contraindications, and 50 were not done for other reasons. As with the left ventriculograms, analyses for efficacy endpoints were repeated, including and excluding studies completed within the prespecified 5- to 14-day window. Since the results were no different in terms of the treatment com-
parison, results are presented only for patients with studies within the time window.

**Hemorrhagic Measurements**

Bleeding observed during the hospital stay was defined as follows: mild if it was of no clinical consequence, did not require transfusion, or resulted in a total blood loss of <250 mL; moderate if 250 to 500 mL of blood loss was observed; severe if any of the following events occurred: >500 mL of blood loss necessitating a transfusion, intracranial bleeding, or gastrointestinal or other external or internal bleeding causing hypotension and requiring emergency transfusion. The site of bleeding, baseline and nadir hematocrit, and packed red blood cell transfusion were recorded for all patients.

**Clinical End Points**

A composite clinical end point was constructed before the study based on a composite of end points considered most important by a survey of cardiologists. This end point consisted of death from any cause, stroke, nonfatal reinfarction, emergency revascularization, development of new heart failure or pulmonary edema, or significant recurrent ischemia. All of these end points were carefully monitored during and after the study enrollment because the study was not blinded. Stroke was defined as a new focal neurological deficit lasting at least 24 hours or documented to correspond to a finding at computed tomographic or magnetic resonance imaging if the patient died before 24 hours. Strokes were further subclassified as hemorrhagic or nonhemorrhagic. New heart failure was defined as the development of new signs and symptoms of pulmonary congestion documented by chest radiograph if available or evidence of inadequate perfusion (hypotension >1 hour or requirement for intravenous inotropic medication to maintain a systolic blood pressure >90 mm Hg) persisting for >1 hour in the setting of adequate filling pressure. Because of the subjective nature of this end point, each case was reviewed in detail by an independent study monitor blinded to treatment collecting information on physical exam, chest radiograph, medical intervention, and hemodynamic findings. Recurrent ischemia was defined as symptoms compatible with myocardial ischemia associated with new ST-segment or T-wave changes on the electrocardiogram. These cases were also reviewed independently by a study monitor.

**Statistical Methods**

Randomization by the Coordinating Center at Duke University was completed in blocks within each study site. Case report forms were completed by the clinical research nurse coordinators and reviewed by the principal investigators before submission to the Coordinating Center. The data were verified independently by study monitors through review of the clinical records. The Data and Safety Monitoring Board met regularly during the study to review the clinical outcome of the patient population.

Continuous baseline and outcome variables are summarized by the median and interquartile range (25th to 75th percentiles), and discrete variables are expressed as percentages; 95% confidence intervals are calculated for major clinical outcomes. The statistical significance of the effect of the treatment on continuous variables was assessed by use of the Wilcoxon rank-sum test. The likelihood ratio $\chi^2$ statistic was used to examine treatment effects for discrete variables. If low event rates precluded the use of a $\chi^2$ statistic, Fisher’s exact test was used.

The sample size was calculated to provide adequate numbers of imaging studies to detect at least a 4-unit improvement in left ventricular ejection fraction. A total of 122 patients with completed studies per group provides 80% power with an $\alpha$ of 0.05, assuming an SD of the measurement of 11 units. Similarly, the study had adequate power (80%) to detect a 33% reduction in thallium infarct size with a total sample size of 210 patients, assuming a mean infarct size of 16% of the left ventricle in the control group and an SD of 13%. Similarly, a 25% reduction in infarct size would require a total sample size of 362 patients with 80% power. The study was not designed primarily to detect differences in clinical end points, but these were examined to provide perspective on the imaging end points.

**Results**

**Patient Characteristics**

The number of patients treated in each group and their respective baseline clinical and angiographic characteristics are listed in Table 1. The population is reflective of the characteristics sought for the study. There were no substantial differences in baseline characteristics.

Table 2 demonstrates the baseline characteristics of patients with and without left ventriculographic and thallium infarct sizing studies within the prespecified time windows. As expected, patients undergoing follow-up left ventriculography were younger and had less severe disease before randomization, while no such bias was evident with regard to thallium studies, although the mortality rates were much higher in patients without follow-up studies for obvious reasons. The mean time until ascertainment of thallium (Fluosol, 7.2±1.5 days; no Fluosol, 7.2±1.4 days) and catheterization (Fluosol, 8.6±2 days; no Fluosol, 8.5±2 days) studies was almost identical in the two groups.

**Primary End Points**

The global LV ejection fraction for the entire population as well as those experiencing an anterior MI is...
shown in Fig 1. No significant difference was seen between patients receiving and not receiving Fluosol. Infarct zone regional wall motion for all patients and for those with anterior MI is shown in Fig 2. Again, no significant difference was seen between patients receiving Fluosol and those not receiving Fluosol. Statistical adjustments for time from chest pain onset to treatment and for time from treatment to left ventriculography did not alter the results of the treatment comparison.

Thallium infarct size, measured as the percentage of LV damage, is shown in Fig 3 for the entire population as well as for those with anterior MI. No significant difference was noted after Fluosol compared with no Fluosol for the entire population. A trend toward smaller mean infarct size was seen in the Fluosol patients with anterior MI, but the median infarct size was larger in this group and no such trend was observed in measures of global or regional LV function.

The coronary angiographic outcomes are demonstrated in Table 3. No differences were observed in the proportion of patients with patent infarct-related arteries or in the TIMI grades at the time of the first cardiac catheterization.

The frequency of clinical outcomes and 95% confidence intervals are displayed in Table 4. Although the primary composite end point was not significantly different between the two groups, a definite increase in heart failure and a trend toward higher death and stroke rates were seen in the Fluosol group, while a reduction in recurrent ischemia and a tendency for less reinfarction were also evident.

The frequency of secondary clinical outcomes is displayed in Table 5. No significant differences were observed in any of the major outcomes reflecting arrhythmia, hypotension, or secondary organ dysfunction. A significant increase in findings consistent with pulmonary congestion was present in the Fluosol group, although these findings resolved within 2 to 3 days and did not lead to an increase in the need for mechanical ventilation. Conversely, a substantial decrease in findings of recurrent ischemia was present in the Fluosol group.

The relation between Fluosol administration and selected hematologic measures is demonstrated in Ta-
Fluosol administration was associated with significant preservation of fibrinogen, a lower platelet count, and no difference in leukocyte count. Measures of anticoagulation, the activated partial thromboplastin time and the prothrombin time, were not affected.

Discussion

The major finding of this study is that, despite promising data in several animal models, intravenous Fluosol did not result in reduction in infarct size or improvement in LV systolic function when used in conjunction with intravenous TPA. Fluosol administration was associated with an increase in non-life-threatening pulmonary edema, but these negative effects were offset by a reduction in the rate of recurrent ischemic events. While these findings are disappointing, the heterogeneity of the clinical end point findings and the discordance from the animal model data suggest the need for further research.

The baseline characteristics of the population reflected the careful selection of patients who might benefit without the confounding effects of prior infarction on measurements of ventricular function or infarct size. On the other hand, because of known problems with the administration of intravascular volume required with the Fluosol, patients with very large infarctions and hemodynamic compromise could not be included in the study. The time from symptom onset to treatment was fairly long, but when patients reporting early with anterior infarctions treated within 3 hours were evaluated separately, no effect of Fluosol could be detected.

The reason for the failure of the pharmacological strategy to produce a positive effect on the primary end point is a matter of speculation. One possibility is that reperfusion injury is a laboratory phenomenon that is not clinically relevant because the damage is limited to areas of myocardium that are destined to die eventually anyway. Other randomized trials of agents touted to prevent reperfusion injury (superoxide dismutase or prostacyclin) also reported no effect on LV function in the setting of angioplasty or thrombolytic therapy for the treatment of acute MI. A second possibility is that the particular regimen used was not effective. The dose that was chosen was based on weight-adjusted effective animal model doses. The protocol required supplemental oxygen administration to all patients because of...
TABLE 6. Hematologic Values

<table>
<thead>
<tr>
<th>No Fluosol (n=217)</th>
<th>Fluosol (n=213)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelets, x1000</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>272 (230,323)</td>
</tr>
<tr>
<td>3 days</td>
<td>224 (176,259)</td>
</tr>
<tr>
<td>Discharge</td>
<td>298 (253,356)</td>
</tr>
<tr>
<td>aPTT, s</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>26 (23,29)</td>
</tr>
<tr>
<td>3 days</td>
<td>54 (42,62)</td>
</tr>
<tr>
<td>Discharge</td>
<td>31 (28,58)</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>307 (265,379)</td>
</tr>
<tr>
<td>4 to 6 hours</td>
<td>205 (146,245)</td>
</tr>
<tr>
<td>24 hours</td>
<td>266 (200,309)</td>
</tr>
<tr>
<td>White blood cell count</td>
<td></td>
</tr>
<tr>
<td>72 hours</td>
<td>8800 (6800;10 100)</td>
</tr>
<tr>
<td>Discharge</td>
<td>8400 (6800;10 100)</td>
</tr>
</tbody>
</table>

aPTT indicates activated partial thromboplastin time. Numbers represent medians (25th,75th percentiles).

the belief that Fluosol enhances tissue delivery of oxygen to ischemic beds. Review of the data indicated good compliance with the use of supplemental oxygen and no difference in the estimate of effect in patients who were compliant. The route of administration could also be questioned. The majority of the animal model work and the one positive human study administered the drug through the intracoronal route during angioplasty. This approach has two advantages: it ensures that the agent is on board before reperfusion with its associated “burst” of toxic metabolites, and it allows for concentrated delivery of Fluosol to the area of infarction without risk of volume overload. Despite these caveats, we felt that the effort to use Fluosol in the setting of intravenous reperfusion would allow for broader application because the majority of reperfusion therapy techniques worldwide use intravenous thrombolytic agents.

The infarct size and systolic function measurements themselves are not perfect. Dropout of sicker patients limits the power and accuracy of the estimate of the effect of Fluosol. However, we found no evidence of a significant treatment effect, regardless of whether all patients with studies were counted or only patients within the prespecified window were included. A slight trend toward fewer large infarcts was present in patients with anterior infarction, although this difference did not reach statistical significance, and the median value and measures of systolic function went in the opposite direction.

The excess rate of congestive heart failure and other evidence of respiratory insufficiency in the Fluosol group was, in part, expected on the basis of the need to administer the Fluosol with a large amount of intravascular volume. Despite the temporary signs and symptoms engendered by the volume challenge, there was no excess of pulmonary congestion after the first day, and no long-term sequelae of this phenomenon could be isolated. During the conduct of the trial in patients with large infarctions, furosemide was administered empirically, and early diuresis was recommended when pulmonary congestion was detected.

One intriguing finding for future research was the reduction in recurrent ischemia and the trend toward reduced reinfarction without any significant increase in the risk of bleeding. Furthermore, laboratory parameters measuring function of the coagulation cascade were not affected. If anything, Fluosol seemed to lead to a sparing of fibrinogen. The poloxamer stabilizer of Flu- osol is known to possess properties associated with reduction in viscosity and increased flow through damaged microcirculatory systems.21 This trial raises the possibility that the vascular “lubricating” effects of the poloxamer could lead to a decrease in recurrent thrombosis of the infarct-related lesion without significantly increasing the risk of bleeding. Further studies are needed to evaluate this issue.

In summary, this trial failed to demonstrate a benefit of Fluosol administration in terms of infarct size reduction or improvement in systolic LV function. The overall clinical effect also was not beneficial, although this conclusion results from an increase in congestive heart failure and a decrease in recurrent ischemia engendered by the drug. Future trials should concentrate on more effective delivery of the drug early in the course, preferably in the setting of a high reperfusion rate as with the use of direct coronary angioplasty. Until further well-controlled clinical trials are completed, the clinical relevance of the laboratory concept of reperfusion injury, and specifically of the adjunctive use of a perfluorochemical, remains speculative.

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References


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