Cost-effectiveness of emergency intraarterial intracerebral thrombolysis: a pilot study.

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Cost-effectiveness of Emergency Intraarterial Intracerebral Thrombolysis: A Pilot Study

Charles F. Lanzieri, Robert W. Tarr, Dennis Landis, Warren R. Selman, Jonathan S. Lewin, Lee P. Adler, and J. B. Silvers

PURPOSE: To assess the clinical efficacy and cost-effectiveness of emergency thrombolysis as a treatment strategy for thromboembolic intracerebral events. **METHODS:** Thirty-four patients with symptoms suggestive of middle cerebral artery occlusion were included. Eight of these patients were treated with intraarterial urokinase. Effectiveness was determined by comparing the admission National Institutes of Health stroke score to the 24-hour National Institutes of Health stroke score. The cost and length of stay of both populations were derived and used as measures of direct cost. The likelihood of admission to extended care facilities and estimated length cost of admission was used as a measure of indirect cost. **RESULTS:** The control population became slightly worse, with a change in National Institutes of Health score of −0.5, whereas the treated population improved slightly, with a change in National Institutes of Health score of +5.12. Analysis of the direct costs data between the two populations revealed a slight increased mean for the treated population ($15 202) as compared with the control population ($13 478). The unpaired *t* test, however, revealed no significant cost difference between the two groups. By reducing the number of completed strokes by one third or by decreasing the severity by the same factor (as shown in our study), the likelihood of admission to an extended nursing facility also is decreased. The cost saving per patient from extended care facilities is approximately $3435. **CONCLUSION:** The emergency application of intraarterial thrombolysis with urokinase results in a statistically significant positive change in National Institutes of Health score by at least five points. A statistically significant benefit is realized through the use of intraarterial urokinase. A statistically insignificant additional cost is shown by this study. This insignificant cost is more than offset by the saved nursing home costs.

Index terms: Economics; Brain, infarction; Thrombolysis

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A large recent review of thromboembolic stroke in the United States (1) finds stroke to be the third leading cause of death in the United States, second to ischemic heart disease and cancer. There are 500 000 new cases each year, and there were 3 million survivors in 1992. Most survivors were disabled. This series estimates the combined direct and indirect costs of stroke in the United States to be $15 billion. At the same time, there seems to be a rather remarkable apathy on the part of health care professionals and the general public toward the acute nature of stroke (2). Cerebral infarctions generally are regarded as irreversible events from which there is little hope of complete recovery. This is counter to the medical professional and general public attitude toward acute ischemic heart disease, which is regarded as a medical emergency and treated as such in the United States.

University Hospitals of Cleveland recently began a program to encourage immediate action in the setting of thromboembolic cerebral infarction. This program included education of the general public, education of emergency medi-

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cal service personnel, education of emergency department personnel, and committed participation from several neuroscience departments. The purpose of the present study was to judge the efficacy and cost-effectiveness of the method compared with control patients. In addition, we hoped to derive direct cost from the present group of patient admissions treated by the same group of physicians during the same period of time at the same institution. We also hoped to project indirect cost for this group. Using this information, we hoped to judge cost-effectiveness and propose a method for future use to judge the cost-effectiveness of other strategies for cerebrovascular thrombolysis in the setting of acute thromboembolic infarction.

Methods

Between October 1993 and September 1994, more than 60 patients were entered into a treatment protocol for the use of intraarterial urokinase (Abbokinase; Abbott Laboratory, Chicago, Ill) in the setting of acute ischemic cerebral infarction. Patients or relatives gave consent, with treatment being offered on a compassionate-use basis. Selection criteria for inclusion in the study included (*a*) clinical examination suggesting a large cerebral vessel occlusion; (*b*) computed tomography of the brain that failed to show evidence of hemorrhage or infarction; (*c*) cerebral angiogram demonstration of vessel occlusion compatible with the patients clinical symptoms; and (*d*) less than 6 hours of elapsed time since the initial symptoms. The initial neurologic examination was performed and rated using the 15-criteria, 42-point National Institute of Neurologic Disease stroke scale (3). This method has been validated previously in the assessment of acute stroke and is in widespread use (4, 5). A four-point improvement generally is considered a significantly positive result (4, 5). Serum-clotting factors and fibrinogen levels also are evaluated at the time of admission. The protocol does not include systemic heparinization before angiography.

Via a 7F femoral sheath, a 6F guiding catheter is placed into the internal carotid system or common carotid artery on the affected side. A Fast Tracker (Target Therapeutics, Fremont, Calif) is navigated to the occluded vessel. This is accomplished under fluoroscopic control, usually with the aid of a Seeker guide wire (Target Therapeutics). The end-hold microcatheter is navigated into the occlusion and, if possible, beyond the occlusion into a patent distal vessel. At this point, 250 000 U urokinase is reconstituted using 5 mL of sterile water. A 50 000-U dose is infused as a bolus distal to the clot. The microcatheter then is withdrawn into the clot where 0.1-mL boluses (5000 U) are administered over a 5- to 10-minute period. The catheter is withdrawn slowly through the clot during these injections. The course of thrombolysis is followed by frequent contrast injections through the base catheter or through the microcatheter. The catheter then is withdrawn proximal to the clot, and 250 000 U are dripped in over a 20-minute period. The total dose into an occlusion does not exceed 1 million U. If multiple thrombi are encountered, the procedure is repeated, but a total dose of 1 500 000 U is not exceeded. After angiographic thrombolysis, a postangiographic computed tomography is obtained to assess for the presence of hemorrhage. Patients are admitted to the neurosurgical intensive care unit for at least 24 hours. Systemic heparinization is used after thrombolysis. The femoral sheath is removed when fibrinogen levels have returned to the normal range. Repeat neurologic examination and assessment of the stroke scale are performed at 24 hours.

For the present study, to avoid ambiguity and to match controls and treated population better, only patients with ischemic symptoms referable to the middle cerebral artery territory were included. This was the most common distribution for strokes. The neurologic status is somewhat easier to quantify for this group of patients. The symptoms of middle cerebral artery territory stroke seemed to be recognized most easily by patients and family members so that these patients arrive at the emergency department in a more timely manner, allowing for rapid treatment.

Several patients were treated for infarction outside the middle cerebral artery territory. These were not included in the present series of patients. Patients also are excluded for age criteria when they are younger than 18 years or older than 80 years. Patients are excluded for a diastolic blood pressure greater than 130 mm Hg, recent surgery or lumbar puncture, history of gastrointestinal or genitourinary bleeding, probable lacunar disease, probable dementia, or probable conversion reaction.

From the more than 60 patients initially entered into the stroke protocol, 34 were eventually proved to have middle cerebral artery thromboembolic disease either by angiography, by clinical means, or by change in the computed tomography or magnetic resonance exam. Eight of these patients were treated within the protocol guidelines with intraarterial urokinase. The most frequent exclusionary criteria were delay of more than 6 hours since ictus, age, and angiographically occult occlusion.

This allowed separation of the 34 patients into a control group of 26 patients and a treated population of 8 patients. The change in the National Institutes of Health (NIH) stroke score between the initial evaluation and the 24-hour evaluation was compared for both groups. This was used as a measure of effectiveness. The hospital costs, both direct and indirect, as well as the hospital length of stay were used as a measure of cost for both groups. These were compared. Because we wanted to assess the total cost to a theoretical vertically integrated health care system, we determined the risk of nursing home admission and estimated the projected costs of extended nursing care in a nursing home for this population. We used the method used by Adelman (6) of projecting the US government census data from 1985 and adjusting for inflation using conservative assumptions.

TABLE 1: Outcome analysis of the control population

Patient	Admission NIH Score	24-h NIH Score	Change in NIH Score	Cost, $	Length of Acute Hospital Stay, d
1	5	5	0	4 412	3
2	3	3	0	5 464	3
3	19	28	−9	11 057	8
4	5	3	2	14 887	13
5	10	20	−10	8 880	4
6	11	7	4	6 199	4
8	25	33	−8	16 258	9
9	4	4	0	6 741	2
10	12	14	−2	11 122	10
12	4	0	4	16 627	10
13	5	13	−8	17 573	14
14	6	3	3	14 813	13
15	9	6	3	17 178	14
16	14	13	1	11 421	6
17	4	4	0	15 583	13
20	2	2	0	7 983	6
21	5	3	2	15 728	8
22	3	1	2	7 671	4
23	6	2	2	59 183	47
24	4	16	−12	11 428	7
25	28	20	8	13 908	10
26	2	0	2	16 333	9
27	22	25	−3	3 477	5
28	6	0	6	5 983	2
34	8	8	0	10 645	9
35	11	11	0	19 897	14
Mean	8.9	9.4	−0.5	13 478	9.5

Results

The introduction of new acute treatments for stroke requires a method for acute stroke assessment at the clinical level. The 15-item NIH neurologic stroke scale was used. In the control population (Table 1), the average initial NIH stroke score was 8.9. In this control population, there was deterioration to a stroke score of 9.4 at 24 hours, with an average change of −0.5. This control figure was compared with the improvement in the treated population (Table 2). The average treated patient entered with an NIH stroke score of 15.6, with improvement to 10.5. This is an average improvement of 5.125. An improvement of four points on the stroke scale is considered a major change in neurologic status equivalent to restoration of vision, speech, or major motor function. These clinical results were compared for statistical significance with the unpaired *t* test, and a *P* value of .0088 (Table 4) was obtained. Thus, we observe a statistically and clinically significant improvement in the treated population when compared with the control population.

TABLE 2: Outcome analysis of the treated population

Patient	Admission NIH Score	24-h NIH Score	Change in NIH Score	Cost, $	Length of Acute Hospital Stay, d
7	9	3	6	14 265	16
11	18	17	1	16 627	14
18	30	20	10	18 066	7
19	7	0	7	14 332	6
30	16	4	12	10 664	7
31	24	34	−10	17 735	7
32	8	4	4	10 065	9
33	13	2	11	19 865	20
Mean	15.6	10.5	5.125	15 202.38	10.75

TABLE 3: Outcome analysis of matched control subjects

Patient	Admission NIH Score	24-h NIH Score	Change in NIH Score	Cost, $	Length of Acute Hospital Stay, d	Where Discharged
Treated						
7	9	3	6	14 265	16	Home
11	18	17	1	16 627	14	Home
18	30	20	10	18 066	7	Home
19	7	0	7	14 322	6	Home
30	16	4	12	10 664	7	Home
31	24	34	−10	17 735	7	ECF
32	8	4	4	10 065	9	Home
33	13	2	11	19 865	20	Home
Mean	15.6	10.5	5.125	15 201.125	10.75	
Matched Controls						
3	19	28	−9	11 057	8	ECF
8	25	33	−8	16 258	9	ECF
10	12	14	−2	11 122	10	Home
14	6	3	3	13 813	13	Home
15	9	6	3	17 178	14	Home
17	14	13	1	15 583	13	Home
25	28	20	8	13 908	10	ECF
34	8	8	0	10 645	9	Home
Mean	15.125	15.625	−0.5	13 695.5	10.75	

Note.— ECF indicates extended care facility.

Because the results indicated we had been treating a disproportionate number of larger strokes than what occurred in the control population (average initial NIH score equal to 15.6 versus 8.9), a small matched control group was chosen from the original group (Table 3). The data in Table 3 have been sorted in chronologic order but contain matched control data for the two populations such that the beginning NIH score in the treated population is approximately equal to the admitting NIH score in the matched controls. Again, a marked improvement in the NIH score at 24 hours is observed. Unfortunately, a valid statistical paired test could not be performed on such a small group of patients. The treated patients had one third the risk of being admitted to extended care facilities compared with their matched controls.

The average length of stay was not significantly different between the control population and the treated population, as seen comparing Table 1 and Table 2; in both cases, a length of stay of approximately 9.5 days is obtained. Again, in the matched controls (Table 3), the length of stay is exactly the same at 10.75 days.

The cost of the initial stay in these two populations also was compared. The average cost to serve the control population was \$13 478, whereas the average cost to serve the treated population was \$15 202. The unpaired *t* test for

TABLE 4: Unpaired *t* tests for NIH scores and cost

	NIH Score Change		Costs	
	Controls	Treated	Controls	Treated
No. of Subjects	26	8	26	8
Mean	−0.5	5.125	\$13 478	\$15 202
Standard Deviation	5.022	7.14	10 418	3525
Standard Error	0.985	2.524	2043	1246
Mean Difference	5.625		1 723.49	
Unpaired *t* value	2.5		.456	
P value	.0088		.6517	

TABLE 5: Outcome analysis of projected nursing home costs

Average days of care for cerebral/vascular disease*	
Men > 65 years of age:	191 d
Women > 65 years of age:	193 d
Mean	192 d
Cost of an extended care bed in Ohio†	
$13 181/y	
$1 099/mo	
Cost of nursing home care/stroke	
$1 099/mo ×1/30 mo/d × 192 d = $7 033	
Adjusted for 3% inflation since 1985 = $10 411	

Sources:

* Health Care Financing Review, Vol. 10, No. 2 HCFA Pub. No. 03276 Washington, U.S. Government Printing Office, Feb 1989.

† National Nursing Home Survey; 1985 U.S. Summary Hing E. Sekscenski E. Vital and Health Statistics Series 13, No. 97, DHHS Pub. No. (PHS) 89-1758, Public Health Service Washington U.S. Government Printing Office, June 1989.

costs, however, revealed a *P* value of .65 (Table 4), indicating that this apparent increase in cost is not statistically significant.

The projected expenses for extended nursing care were calculated from US government census data, using a conservative estimate of 3% inflation in nursing home cost annualized over the 10 years since the last census in 1985. Table 3 suggests that the likelihood of extended care facility admission after middle cerebral artery distribution stroke is three times greater for the matched control population. Because the vast majority of patients in this study were older than 65 years, we used the numbers for this population when calculating the nursing home costs.

As Table 5 indicates, the average days of extended nursing care required for cerebrovascular disease based on US government data are 192 (7). The cost of an extended care bed in the state of Ohio is approximately $1099/mo (8). Using the 1985 data, an estimated cost per stroke of $7033 is generated. Adjusting for inflation, the average nursing home cost for stroke in the present day is $10 411.

Discussion

The results shown in our investigation indicate a remarkable and statistically significant improvement in clinical status relative to the control population. There was successful angiographically confirmed clot lysis in all eight patients treated by intraarterial urokinase. All patients were treated within 6 hours. Although one of our patients deteriorated clinically, there were no hemorrhages in this group.

Estimates of the cost of stroke to a general population are difficult and many assumptions are required (9). A method of deriving direct and indirect costs of stroke has been proposed (9) that combines the direct cost of hospital charges, drugs, physician charges, and so forth with indirect costs of morbidity and mortality.

Direct Costs

Our results indicate that the direct cost for intraarterial urokinase therapy is slightly higher than that for the control population. Again, this direct cost was determined to be statistically insignificant using our group of patients. We believe that the indirect cost savings are likely to be greater and statistically significant compared with the slightly increased direct cost shown in our population. Although our determination of direct cost shows a statistically insignificant increase for the treated population, we postulate that the direct cost will be shown to be significantly higher when a larger population is studied. This slight increase in direct cost should be regarded as an investment in larger cost savings to be realized in later years of the patient's life. Although a discussion of the concept of net present value is beyond the scope of this study, suffice it to say that there is a time value to money: a dollar saved today is worth considerably more in the future. The exact amount of savings is based on the opportunity cost or discount rate and the number of periods forward one estimates. Thus, savings of indirect cost lasting years into the future are worth considerably more in current dollars in direct costs, and this large figure must be compared with the small increase in direct costs that we have shown.

Cost-effectiveness

Although there may not be direct cost savings shown by our group of patients, the method is, nonetheless, cost-effective. We propose the following method for evaluating cost-effectiveness in the future, as well as current thrombolytic strategies, based on changes in the NIH score in the initial 24 hours measured against the change in mean direct cost to attain that effect.

Cost-effectiveness

$$= \frac{\text{Cost}}{\text{Effectiveness}}$$

$$= \frac{\text{Cost}_{\text{treated}} - \text{Cost}_{\text{controls}}}{\text{Change NIH Score}_{\text{treated}} - \text{Change NIH Score}_{\text{control}}}$$

$$= \frac{15\,202 - 13\,478}{5.125 - (-0.5)}$$

$$= 307$$

To calculate the cost-effectiveness in the control population, one would divide the mean direct cost by the mean improvement in NIH score. The cost-effectiveness ratio in the control group would be equal to −26 956. The cost-effectiveness ratio for the treated population would be 307. Thus, there is a remarkable cost-effectiveness to the present method of intraarterial urokinase. We would like to suggest that the cost-effectiveness of other strategies for the treatment of acute stroke be determined by this or a similar determination of ratio. This should be used as one of the many tools for determining the desirability of a given technique. One should strive for improvement in the denominator (effectiveness) and the numerator (cost) separately, and not at the expense of one in favor of the other.

Indirect Cost

The indirect cost of stroke includes a current portion of indirect cost comprising nursing care, rehabilitation, appliances, and so forth, and a long-term portion of indirect cost including lost wages caused by disability and the cost of early demise expressed as lost wages or the inability to perform activities of daily living. Ideally, one also would want to include an estimate of quality-adjusted life years expressed as a monetary figure. There are no known studies estimating the value of quality-adjusted life years related to a change in the 24-hour NIH stroke scale of five points. We believe this value would be relatively large; once determined as a change of five points in the stroke scale, it could mean the difference between vision and blindness, speech and aphasia, or other important neurologic functions. We have estimated the current portion of the indirect costs from regional nursing home data at approximately $10 000 (Table 5). The treated population was one third as likely to be admitted to extended care facilities. The most powerful predictor of functional recovery and eventual nursing home discharge is the initial severity of the stroke (10). Alexander (10) found that the higher the functional status on admission to rehabilitation, the shorter the duration of extended care hospitalization. Virtually every patient in this highly functional group went home regardless of age, the other important independent variable. It is clear that functional status at the time of hospital discharge is a powerful predictor of eventual outcome (10), and intraarterial urokinase in the setting of acute stroke improves functional status. By reducing the size of a stroke by one third, one can postulate that a savings of $3435 would be realized in the current portion of the indirect cost expressed in 1994 dollars for each stroke patient. The long-term portion of the indirect cost includes estimates of days of work lost because of disability or premature death. Potential lost earnings could be estimated based on the cost of human capital (6). In the economic impact study on the cost of stroke conducted on 1976 data, the estimated long-term portion of indirect cost is $3.5 billion (based on a discount rate of 6%) and a 1976 incidence of stroke is 400 000. Thus, the long-term portion of indirect cost for each stroke in 1976 is $8750. If, as the current study suggests, we had been able to limit stroke size by one third in 1976, the savings would have been $2887 per stroke, the projected value of which would have been $8240 in 1994 (using a discount rate of 7%, as is common current practice). A total indirect savings per stroke could be derived by adding the current and long-term portion of the indirect cost, yielding $11 675. The current incidence of thromboembolic stroke in the United States is 500 000, with more than 3 million survivors. National annual savings could exceed $5 billion. The net per stroke savings would be the difference between the savings in indirect cost and the slight increase in direct cost or more than $10 000 per stroke.

There are several limitations of study design in this investigation that merit special mention. First, the study was not performed in a randomized manner. Therefore, sample bias in subject versus control selection cannot be completely avoided. The exclusion criteria for the majority of the 34 control subjects was a period greater than 6 hours from the time of ictus to the time of angiography. This factor may have contributed to the overall lower NIH score on admission in the control group, becausd patients with less-severe symptoms may have delayed longer before seeking medical treatment. An additional sample bias may have occurred in those patients excluded from the treatment cohort because of inability to document intraarterial thrombus at angiography.

Although it is impossible to compensate completely for these potential sources of sample bias, an attempt was made to address these issues through creating a second control group that was matched for admission NIH score. Because of the smaller sample size, statistically significant difference in 24 NIH scores could not be proved. However, the results for change in NIH score in this smaller matched group are not changed from those with the larger group, suggesting that sample bias may not have significantly altered the results.

Finally, the construction of an economic model for indirect costs relative to change in the NIH stroke scale also requires several economic assumptions. The observed reduction in nursing home admission is not statistically proved. These have the potential to introduce bias into the calculation of cost-effectiveness. This potential source of error was considered, and very conservative estimates of cost of nursing home care per stroke were used in an attempt to decrease this potential source of bias.

Conclusion

For the vertically integrated health care system providing capitated coverage, including long-term nursing care, and for third-party and government payors, the aggressive treatment of acute stroke is a financially sound decision (11). For patients wanting to improve their likelihood of good quality of life, provider systems that aggressively treat acute stroke are desirable. For the nation as a whole, especially government agencies granting funds for scientific research, investment in programs that seek to improve the outcome of acute stroke is desirable.

There are several areas in which improvement could be realized. Increased educational efforts of the general public, emergency medical service, and clinicians would increase the opportunity to treat stroke patients within the critical initial hours. A paradigm shift regarding stroke is required. Stroke should be regarded as an acute medical event requiring rapid action, rather than an irreversible step into chronic illness and disability. Multiple and parallel comparative studies are required to evaluate the best sort of emergency therapy for acute stroke. Additional trained interventional neuroradiologists will be required to meet the demand for acute stroke therapy. Programs that train high-quality interventional neuroradiologists should be enthusiastically supported. The NIH and the Food and Drug Administration should expedite the funding of research in this vital area and should expedite the rapid dissemination of new technology and ideas.

Finally, a more detailed model of indirect cost of stroke in the United States is needed. This should include standardized costs for nursing homes, lost wages, and quality-adjusted life years in the stroke population. Such a model would allow statistically significant conclusions to be drawn.

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