Cost-Effectiveness Analysis of Tissue Plasminogen Activator for Acute Ischemic Stroke: A Comparative Review

Mei-Chiun Tseng and Ku-Chou Chang

Abstract-

Purpose: This work was undertaken to review current evidence of cost-effectiveness analysis (CEA) on thrombolysis for acute ischemic stroke.

Methods: An electronic search via PubMed, from 1995 until May 2004, was performed. The methods undertaken by these studies were examined with particular attention to their modeling assumptions, sources of data, and outcome measures.

Results: Three comprehensive CEAs of rtPA (recombinant tissue plasminogen activator) for acute ischemic stroke were reviewed. These studies were from the United States, Canada, and the United Kingdom. All these studies employed the perspective of a healthcare system and used a Markov decision-analytic modelling approach. Estimates of effectiveness of rtPA were based on the National Institute of Neurological Disorders and Stroke (NINDS) rtPA Stroke Trial, literature-derived values or a stroke registry. In each study, functional outcome measured by the modified Rankin Scale was used to represent health states, and quality-adjusted life year gained was the health outcome summary measure. The cost-effectiveness of rtPA therapy varied in magnitude, but seemingly with same positive implications.

Conclusions: Cost-effectiveness analysis requires information on an intervention's effectiveness and country-specific sources of epidemiological and resource utilization data, most of which are not yet available in Taiwan. Despite the limitations, CEA is essential if a healthcare system would like to contain costs while maintaining, or improving, quality of care.

Key Words: Review, Cerebral infarction, Tissue plasminogen activator, Costs and cost analysis

Acta Neurol Taiwan 2004;13:149-155

INTRODUCTION

Intravenous recombinant tissue plasminogen activator (rtPA) therapy for patients admitted within 3 hours from onset of ischemic stroke has been shown to improve outcome in acute stroke patients, though there is still much discussion about the associated magnitude of risks, costs and benefits[1]. Given an increasing requirement for the economic evaluation of health care interventions to be considered in formulating and implementing guidelines for clinical practice, cost-effectiveness of medical services is receiving greater attention in

From the Department of Business Management, National Sun Yat-Sen University, Kaohsiung, Taiwan; First Department of Neurology, Chang Gung Memorial Hospital, Kaohsiung, Taiwan.
Received June 9, 2004. Revised June 18, 2004.
Accepted July 26, 2004.

Reprint requests and correspondence: Ku-Chou Chang, MD. First Department of Neurology, Chang Gung Memorial Hospital; Niao-Sung Hsiang, Kaohsiung, Taiwan.
E-mail: changkcc@ms24.hinet.net

recent years. Of equal concern is that economic evaluations need be justified in every country because clinical practice patterns and the level of healthcare resources used could vary from country to country.

There is a growing need for cost-effectiveness analysis (CEA) of stroke service in Taiwan facing the enormous demand on limited health resources. The need is even greater after the availability of new costly thrombolysis therapy for acute stroke. However, not much is known about the economic evaluation of stroke care in Taiwan. A compact review of current published CEAs of rtPA for acute stroke may not only help clinicians to clarify the impact and limitations of the most updated information, but also shed some light on the future research in Taiwan.

The purpose of this article is to summarize current evidence of CEAs on thrombolysis with rtPA for acute ischemic stroke. This review is led by two questions: first, what is the current evidence regarding the economic impacts of rtPA for stroke; and, second, how were the published studies on the CEAs of rtPA for stroke conducted ? We focused on cost-utility analysis, which is a special variant of CEA[2]. For review on a broad economic evaluation in stroke research we refer to Evers et al.[3].

METHODS

An electronic search of English medical literature via PubMed, from 1995 until May 2004, was performed using the keywords: stroke, tissue plasminogen activator, and cost. Additional studies were sought among citations of papers retrieved as a result of the electronic search. However, no intention was made for complete systematic review.

In this review, our approach is to examine the methods undertaken by each of these CEAs with particular attention to their different modeling assumptions, compare their sources of data along with the outcome measures. We also discuss underlying specifications that we thought could result in great differences between these CEAs.

RESULTS

There were three comprehensive CEAs of rtPA for acute ischemic stroke. These provided cost-effectiveness of rtPA for acute ischemic stroke for three different countries: the US[4], Canada[5], and the UK[6,7]. All of these studies employed the perspective of the healthcare system, rather than a societal perspective. Because national healthcare systems in different countries appear diverse, the components of cost evaluated by these studies differ markedly. The US study included costs of inpatient, rehabilitation, and nursing home facilities. In the Canadian study, only direct medical costs incurred for management of acute and recurrent ischemic stroke were considered. By contrast, the UK study took a broad perspective to include the long-term care which may fall either to the National Health Service (NHS) continuing care sector or to the social service budget. Main characteristics of each of these studies are summarized in Table 1.

Table 1. *Summary of cost-effectiveness studies of rtPA for acute ischemic stroke*

Study	Perspective	Methods	Measure (% discount rate)		Main source of clinical data
			Costs	Benefits	
Fagan et al.[4]	US healthcare system	Markov modeling Monte Carlo simulation Time horizon: 30 y	Direct costs (5% per year)	QALYs (5% per year)	NINDS rtPA Stroke Trial
Sinclair et al.[5]	Canadian healthcare system	Markov modeling Monte Carlo simulation Time horizon: 30 y	Direct costs (5% per year)	QALYs (3% per year)	NINDS rtPA Stroke Trial
Sandercock et al.[6,7]	UK NHS and personal social services	Markov modeling Monte Carlo simulation Time horizon: lifetime	Direct costs (6% per year)	QALYs (6% per year)	Cochrane systematic review and data from the Lothian Stroke Register (LSR)

QALY indicates quality-adjusted life-year.

The first comprehensive CEA of rtPA for acute ischemic stroke was published in 1998 by Fagan et al.[4]. Several authors of this US study were involved in the NINDS rtPA Stroke Trial. The subsequent study was undertaken in Canada[5], in which the leading author of the US study was also involved. The recently published UK study[6] was based on a funded project[7] of the NHS R&D Health Technology Assessment (HTA) Programme in the UK.

Modelling techniques

All these studies used a Markov decision-analytic modelling approach to perform the CEA of rtPA for stroke. Briefly, a Markov decision-analytic model was created to describe outcomes associated with two different treatments: rtPA treatment versus current standard stroke care without rtPA. A Markov model consists of a set of mutually exclusive and collectively exhaustive health states, usually referred to as Markov states, occurring from the index stroke to death or end of the time horizon of the analysis. In any given interval of time, usually referred to as a cycle or stage, a cohort member is in one and only one of the states. There are transition probabilities which characterize how a cohort member may pass in successive cycles. Those state-transition probabilities are time-variant, and are used to redistribute the membership of a state from one stage to the next.

In the US study[4], and similarly in the Canadian study[5], a hypothetical group of 67 years old patients eligible for rtPA therapy for ischemic stroke were hospitalized. During hospitalization, patients had different risk of symptomatic intracranial hemorrhage (ICH) or death according to whether rtPA therapy was chosen. These hypothetical patients at discharge were stratified by level of functional disability which is measured by the modified Rankin Scale (mRS). Disposition status (home, rehabilitation centers, or long term care facilities) was subject to the score of mRS at discharge. After 1 year, deaths in different health states were assumed to occur at an equal rate. Transitions to lower health states, including death, occurred only because of recurrent stroke. Patients who experienced a recurrent stroke might either retain the existing health states or became worse. Stroke recurrence rate was assumed to occur at an equal rate across the health states considered, so was the case fatality of patients with recurrent stroke. Overall, probability estimates within the first year were based on data of NINDS trial, while for subsequent years, they were based on literature.

Consistent with the other two studies, Sandercock et al.[6,7] also chose 1 year as a cycle for analysis. However, in this study, surviving patients were categorized as independent (mRS 0-2) or dependent (mRS 3-5). The time horizon considered was lifetime in the UK study[6,7], but was 30 years in both the US[4] and Canadian[5] studies.

Data sources

In the studies done in the US[4] and Canada[5], the estimates of efficacy of rtPA and the outcomes (with or without rtPA therapy) within the first year were largely based on the NINDS rtPA Stroke Trial. After the first year, annual stroke recurrent rate (5.2%) and annual case fatality rate due to recurrent stroke (19%) were estimated based on literature-derived values.

Because more efficacy data are available nowadays, the estimates of efficacy in the UK study[6,7] were able to be based on a systematic review of all relevant randomized trials[8], and supplemented by data from a local stroke registry, the Lothian Stroke Register (LSR). At the time the CEA was undertaken, the LSR contained data from 1,779 prospectively identified consecutive patients with a definite or probable stroke admitted, from September 1989 to June 2000, to the study hospital in Edinburgh, Scotland. Specifically, the LSR data items used in the analysis included length of hospital stay, the mRS, the occurrence of recurrent stroke, death from recurrent stroke, and death from all causes up to 12 months after the index stroke.

Outcomes considered

As mentioned above, all the studies reviewed were undertaken from a healthcare system perspective, and thereby included only direct costs. However, some variations in the cost-items included were noted. For example, the US study[4] included nursing home costs, and assumed that patients admitted to a nursing home would continue to reside there until death. Future costs were discounted at an annual rate of 5% in both the US[4] and

the Canadian[5] studies, but 6% in the UK study[6,7]. As the healthcare system in each country is different, it is difficult to compare the additional costs of rtPA treatment among these studies.

All studies reviewed used quality-adjusted life year (QALY) gained as the health outcome summary measure to compare health outcomes that were different in kind. In these studies economically evaluating rtPA treatment, QALYs are calculated by multiplying the utilities associated with different health states by the years of survival. All these studies used functional outcome measured by the mRS to represent health states. The assigned utility values ranged from 0.90 for mRS 0 to -0.02 for mRS 5 in the US[4] study, as well as in the Canadian[5] study. They were 0.74 for functionally independent status and 0.38 for functionally dependent status in the UK study[6,7]. Future QALYs were discounted at various annual rates: 5% in the US study, [4] 3% in the Canadian study[4], and 6% in the UK study[6,7]. The main assumptions and specifications of each study are presented in Table 2.

Sensitivity analysis

The multi-way sensitivity analysis was done by Monte Carlo simulation in both Fagan et al.[4] and Sandercock et al.[6,7] (not specifically reported in Sinclair et al.[5]). While cohort simulation tracks a hypothetical cohort of patients simultaneously through the model, Monte Carlo simulation (first order) tracks a large number of individual patients, and each of them transits

Table 2. *Key parameters and assumptions used in the models*

Study	Baseline assumptions		Utility values	
	Within the first year	After the first year		
Fagan et al.[4]	Age of the index stroke: 67 y NINDS rtPA Stroke Trial data for LOS, ICH rate, discharge disposition, functional outcome, and mortality	Survival: US annual age-specific mortality rates Multiplier for stroke patients, 2.67 stroke recurrence rate per year, 5.2% recurrent stroke mortality per year, 19% No rtPA for recurrent strokes	Rankin 0 Rankin 1 Rankin 2 Rankin 3 Rankin 4 Rankin 5 Death	0.90 0.80 0.46 0.34 0.30 -0.02 0.00
Sinclair et al.[5]	Similar to Fagan et al.	Similar to Fagan et al., Canadian age-adjusted mortality rates, instead	(Similar to Fagan et al.)	
Sandercock et al.[6,7]	eligible patients: 5.3% of admitted patients Lothian Stroke Register (LSR) data for LOS, median survival (21 d for patients dying < 6m, 300 d otherwise), and functional outcome	Survival: UK annual age-specific mortality rates Multiplier for stroke patients, 2.50 stroke recurrence rate per year, 5% recurrent stroke mortality per year, 25% No rtPA for recurrent strokes	Independence Dependence Death	0.74 0.38 0.00

Table 3. *Cost-effectiveness of rtPA for acute ischemic stroke*

Study	Year of costs	Main results	Cost per QALY
Fagan et al.[4]	1996, US $	Over 30 years, per 1,000 eligible patients: 564 additional QALYs cost savings of $4.3 million	Over 30 years, cost-saving of $7,544 per QALY
Sinclair et al.[5]	1999, Canadian $ ($Can)	Over 30 years, per 1,000 eligible patients: 3460 additional QALYs cost savings of $Can3.8 million	Over 30 years, cost-saving of $Can1,098 per QALY
Sandercock et al.[6,7]	1999-2000, UK£	Over a lifetime, per 100 patients treated: 3.63 additional QALYs cost savings of £350, 532	Over a lifetime, cost-saving of £96,565 per QALY

through the model one at a time.

The results of these CEAs of rtPA for acute stroke are summarized in Table 3. The authors' conclusions about cost-effectiveness of rtPA therapy varied in magnitude, but with seemingly the same implications[9].

DISCUSSION

Although modeling in economic evaluation has been increasingly used, the clinical world has been skeptical about the approach[10]. However, even since a couple of major medical journals provided guideline for conducting, reporting, and using such analyses in 1996[11-14], modeling techniques in health economic evaluation have been well accepted, and have even become unavoidable[10]. In addition, the US Panel on Cost-effectiveness in Health and Medicine considered that "failure to use models to extrapolate from primary data can lead to greater error than the models themselves would introduce"[12]. In health economic evaluation, a modeling approach is typically taken in situations where the relevant clinical trials as well as observational data are constrained in terms of the range of outcome data collected, or the length of follow-up. Buxton et al. discussed in great detail why modelling in health economic evaluation is unavoidable[10].

Markov models differ from other models because of the Markovian assumption, which states that the transition probabilities depend only on current health state and not on history of health states[15]. That is to say, it is not possible for a patient's prognosis in a given state to depend on events prior to arriving in the state. However, this assumption can be easily resolved by expanding the number of health states so that each (current) state represents a unique health-state history, and thus should not be taken as a limitation of Markov models.

Naturally, CEA of rtPA for stroke relies crucially on the assessment of the clinical effectiveness of the intervention as well as the course of illness without the intervention. The gold standard for assessing the efficacy of rtPA is randomized double blind controlled trials, such as the NINDS rtPA Stroke Trial. However, there are concerns about the methodological weaknesses or problems of the NINDS trial that could lead to over-estimating the benefits of rtPA[7]. Furthermore, the general applicability of the study population has to be considered when assessing the results of clinical trials and their suitability for economic evaluation[14]. As noted, "there are often trade-offs between the internal validity of data (optimized in randomized trials) and their external validity in actual practice"[12]. For these and other reasons, the UK study chose to rely on different sources that supposedly pertain to UK NHS.

By the nature of the CEA, a comprehensive economic evaluation of rtPA therapy requires comparison of the costs and the consequences of health benefits over an appropriate duration of follow-up. Although the time horizon of an analysis should generally be long enough to capture all the differential costs and effectiveness of rtPA therapy[14], only the UK study[6,7] conducted the analysis over a lifetime. The remaining two studies chose time horizon of 30 years, and emphasized that 90% of the cohort (with index stroke at age of 67 years) had died by that time.

Outcomes in CEAs may be measured in different ways, such as QALY or Health Years Equivalent (HYE)[2]. The concept of the QALY was first developed in the 1960s in a study on chronic renal failure, and has an intuitive appeal as a measure of the value of health outcomes. According to Nord[16], the idea was to combine different outcomes such as saved lives, increases in life expectancy, different kinds of functional improvement, and different kinds of symptom relief to a common value scale, whereby it would be possible to compare these various kinds of outcomes with each other.

Although QALY takes into account both the quantity (years alive) and the quality of life of stroke patients, how the utility values associated with various health states were determined is a major concern. In general, utilities can be elicited from patients or healthy people or assigned by experts[17]. In the UK study[6,7], utilities after stroke were elicited from patients of the LSR cohort through a separate study[18]. By contrast, utility values in the US study[4], and as well as in the Canadian study[5], were assigned according to published results of utility assessments for stroke outcome[19,20]. However, as the published results provided scores for minor, moderate, and severe functional outcome (relative to death) [19], how

the exact utility values for mRS 1 through mRS 5 were determined is not clear (mRS 0 was determined based on another source).

When performing CEA, future outcome measures are usually discounted to reflecting that later values have less impact than earlier ones. However, how one determines a proper discount rate is not clear. Theoretically, the appropriate discount rate to use for costs is the opportunity cost of capital. However, how the health benefits, such as QALYs, should be discounted and whether they should be discounted at the same rates as cost is still debatable. Most of the published economic evaluations in health care used a discount rate of 5% per year, and it remains common practice to discount costs and benefits at the same rate. As shown in Table 1, there are variations in the discount rate chosen in the studies we reviewed, but all are within a reasonable range.

The ideal CEA usually includes sensitivity analysis to assess the influence of varying assumptions, to detect potential problems of data uncertainty, and to explore the general applicability of study results to other settings. The simple form of sensitivity analysis, referred to as a one-way analysis, is to systematically vary estimates for each parameter one at a time over its plausible range of values. A more sophisticated approach, referred to as a multi-way analysis, is to allow more than one parameter to vary within the prespecified plausible ranges. Both approaches are commonly employed[15].

There are other studies addressing economic evaluation of rtPA for stroke but are not include in this review. For example, Hallan et al. evaluated rtPA therapy from the perspective of patients by performing a simple decision analysis[21]. Health outcomes for alternative therapies were calculated in that study, but no healthcare resource utilization was presented. Using a semi-Markov model consisting of two modules (acute care and long-term care/prevention of recurrence among stroke survivors), Chambers et al. also estimated the cost-effectiveness of rtPA in acute stroke in the UK[22]. The study was excluded because the purpose of that article was development of a stroke outcome model, and the time horizon considered in the illustrated CEA of rtPA was merely 5 years.

To conclude, cost-effectiveness research regarding stroke treatment has grown enormously in recent years[23]. CEA results are often of limited general applicability owing to the known differences in stroke care patterns across countries[23], let alone the country-specific sources of epidemiological and resource utilization data. Other limitations of CEA are well acknowledged[11-14,23,24]. Despite the limitations, cost-effectiveness research is essential if a healthcare system would like to contain costs while maintaining, or improving, quality of care.

While the direct cost and length of hospital stay of acute stroke treatment have been evaluated[25,26], the CEA of many stroke treatments to improve health in Taiwan remains untested and therefore unproven. It is hoped that this review will be of assistance to better understanding of CEA studies in general and CEA of rtPA for acute stroke in particular.

ACKNOWLEDGEMENTS

This study was supported by a grant from the National Science Council (NSC91-2416-H-110-027), Taiwan. Authors would like to thank Dr. Harold P. Adams, Jr., Dr. Peter Sandercock, Dr. Werner Hacke and Dr. Graeme Hankey for all the inspirations and encouragement.

REFERENCES

1. Wardlaw JM, Sandercock PA, Berge E. Thrombolytic therapy with recombinant tissue plasminogen activator for acute ischemic stroke: where do we go from here? A cumulative meta-analysis. Stroke 2003;34:1437-42.
2. Evers SM, Goossens ME, Ament AJ, et al. Economic evaluation in stroke research. An introduction. Cerebrovasc Dis 2001;11:82-91.
3. Evers SM, Ament AJ, Blaauw G. Economic evaluation in stroke research: a systematic review. Stroke 2000;31:1046-53.
4. Fagan SC, Morgenstern LB, Petitta A, et al. Cost-effectiveness of tissue plasminogen activator for acute ischemic stroke. NINDS rt-PA Stroke Study Group. Neurology 1998; 50:883-90.
5. Sinclair SE, Frighetto L, Loewen PS, et al. Cost-Utility analysis of tissue plasminogen activator therapy for acute

ischaemic stroke: a Canadian healthcare perspective. Pharmacoeconomics 2001;19:927-36.
6. Sandercock P, Berge E, Dennis M, et al. Cost-Effectiveness of Thrombolysis With Recombinant Tissue Plasminogen Activator for Acute Ischemic Stroke Assessed by a Model Based on UK NHS Costs. Stroke 2004;35:1490-8.
7. Sandercock P, Berge E, Dennis M, et al. A systematic review of the effectiveness, cost-effectiveness and barriers to implementation of thrombolytic and neuroprotective therapy for acute ischaemic stroke in the NHS. Health Technol Assess 2002;6:1-112.
8. Wardlaw JM, del Zoppo G, Yamaguchi T, et al. Thrombolysis for acute ischaemic stroke (Cochrane Review). The Cochrane Library. Oxford: Update Software, 2003:3.
9. Matchar DB. Editorial comment--what can models teach us about stroke treatment? Sorting out the missing bits. Stroke 2004;35:1497-8.
10. Buxton MJ, Drummond MF, Van Hout BA, et al. Modelling in economic evaluation: an unavoidable fact of life. Health Econ 1997;6:217-27.
11. Russell LB, Gold MR, Siegel JE, et al. The role of cost-effectiveness analysis in health and medicine. JAMA 1996;276:1172-7.
12. Weinstein MC, Siegel JE, Gold MR, et al. Recommendations of the panel on cost-effectiveness in health and medicine. JAMA 1996;276:1253-8.
13. Siegel JE, Weinstein MC, Russell LB, et al. Recommendations for reporting cost-effectiveness analyses. JAMA 1996;276:1339-41.
14. Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. BMJ 1996;313:275-83.
15. Sonnenberg FA, Beck JR. Markov models in medical decision making: a practical guide. Med Decis Making 1993;13:322-8.
16. Nord E. Cost-value analysis in health care: making sense out of QALYs. UK: Cambridge University Press, 1999:18.
17. Post PN, Stiggelbout AM, Wakker PP. Utility of health states after stroke: a systematic review of the literature. Stroke 2001;32:1425-9.
18. Dorman P, Dennis MS, Sandercock P. Are the modified "simple questions" a valid and reliable measure of health related quality of life after stroke? J Neurol Neurosurg Psychiatry 2000;69:487-93.
19. Solomon NA, Glick HA, Russo CJ, et al. Patient preferences for stroke outcomes. Stroke 1994;25:1721-5.
20. Mark DB, Hlatky MA, Califf RM, et al. Cost effectiveness of thrombolytic therapy with tissue plasminogen activator as compared with streptokinase for acute myocardial infarction. N Engl J Med 1995;332:1418-24.
21. Hallan S, Asberg A, Indredavik B, et al. A decision analysis of thrombolytic therapy compared with standard therapy in acute ischaemic stroke. J Intern Med 1999;246:549-59.
22. Chambers MG, Koch P, Hutton J. Development of a decision-analytic model of stroke care in the United States and Europe. Value Health 2002;5:82-97.
23. Holloway RG, Benesch CG, Rahilly CR, et al. A systematic review of cost-effectiveness research of stroke evaluation and treatment. Stroke 1999;30:1340-9.
24. Holloway R, Dick AW. Editorial comment--stroke cost-effectiveness research: are acceptability curves acceptable? Stroke 2004;35:203-4.
25. Chang KC, Tseng MC, Weng HH, et al. Prediction of length of stay of first-ever ischemic stroke. Stroke 2002; 33:2670-4.
26. Chang KC, Tseng MC. Costs of acute care of first-ever ischemic stroke in Taiwan. Stroke 2003;34:e219-21.