Thrombolytic Therapy Guided by a Decision Analysis Model: Are There Potential Benefits for Patient Management?

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Summary

Background: Although thrombolytic therapy improves the outcome of myocardial infarction, it is associated with increased risks of stroke and bleeding; these risks may outweigh the benefits of therapy. The risks and benefits of thrombolysis, for any individual clinical situation, can be explicitly estimated by means of decision analysis.

Hypothesis: The aim of this study was to compare the actual use of thrombolytic agents for suspected acute myocardial infarction (AMI) with the management preferred by a decision analysis model.

Methods: Admission data prospectively obtained in 262 consecutive patients admitted to a rural community hospital's coronary care unit with suspected AMI, as well as clinical decisions and outcomes, were reviewed and analyzed.

Results: Seventeen deaths from AMI and no major strokes were observed, compared with 18.30 deaths and 0.85 major strokes predicted by a decision analysis model. Forty-seven of 84 patients with confirmed AMI and 3 of 178 without AMI were given a thrombolytic agent, compared with 65 patients with and 7 without AMI who had decision analysis-guided therapy. Decision analysis-guided therapy could have saved 3.7 additional lives and gained 29.6 life years, but produced 0.4 extra strokes. Changing the quality adjustment for stroke or heart failure would not have altered the treatment preferred by decision analysis in any of the 262 cases studied. Some patients were predicted to benefit considerably from thrombolysis with little extra risk of stroke and vice versa: all cases must, therefore, be assessed individually.

Conclusions: A decision analysis model can guide thrombolytic therapy by promptly defining its risks and benefits.

Key words: decision analysis, thrombolysis, myocardial infarction

Introduction

Several large trials have shown that thrombolytic drug therapy can improve survival after myocardial infarction (MI).^{1–3} However, thrombolytic drugs also increase the risk of a major bleeding episode or stroke, leaving the physician with a potentially difficult choice—to give thrombolytic therapy and take the risk of precipitating a stroke, or to withhold it and take the risk of a preventable death from MI. The decision to administer thrombolytics would not be too difficult if all patients were similar to those who fulfilled the admission criteria for the large clinical trials: that is, middle aged, with definite acute MI, presenting shortly after symptom onset and with no particular risk factors for stroke or bleeding, and, if not thrombolized, would have a mortality rate of around 10%.⁴ Unfortunately, such patients may not always be encountered by physicians in everyday practice. In real life, both the time of symptom onset and the diagnosis of MI are often far from certain, and individual patients may have hypertension, low body weight, advanced age, or other factors that expose them to increased risk of bleeding, stroke, and death.⁵ It is possible, however, to determine explicitly the risks and benefits of thrombolysis by the mathematical technique of decision analysis, provided the probabilities of MI, death from MI, and stroke can be reliably estimated.⁶ This paper proposes the use of a decision analysis model to help the physician decide at the bedside whether and how thrombolysis should be given.

Decision analysis integrates relevant information from a variety of sources to calculate the benefits and risks of an alternative course of action. It is an established technique and can be applied either to individual cases as a guide to clinical decision making or to groups as a guide to policy.⁷

Decision analysis performs the reverse function of large clinical trials: instead of taking the experience of many individual patients and pooling it to determine an overall benefit, it

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takes overall experience and uses it to determine the probable benefit for an individual patient. The technique helps to place all the currently available relevant information on the risks and benefits of thrombolytic therapy in perspective. Although the assumptions and quality adjustments used in decision analysis may be subject to personal opinion, unlike conventional decision making these are explicitly stated.

The currently used alternative to decision analysis is "fast track" triage, which restricts thrombolysis only to patients with "definite" electrocardiographic (ECG) changes.⁸ We have already suggested the use of a decision analysis model to guide thrombolysis of acute MI (AMI).⁹ Such a model, which is constantly updated in the light of new information, and predictive instruments to estimate the risk of infarction, death, stroke, bleeding, and so forth, is being developed in our coronary care unit as a bedside decision support computer program. This study reports our experience with a prototype of this model and explores the potential benefits such a system might have over orthodox clinical decision making and over "fast track" triage.

Methods

The life expectancies of patients with suspected AMI treated with aspirin alone, or with aspirin in combination with streptokinase or "accelerated" TPA, were calculated using a modification of a previously published decision analysis model.⁶ Briefly summarized, this analysis models the chance events and outcomes likely to occur in a patient with possible AMI (Fig. 1). The outcome of such a patient was assumed to

depend on the probabilities of any of the following chance events taking place: death, a major disabling stroke, a major bleed, anaphylaxis, or some other catastrophe. If all these hazards are survived the patient may subsequently develop congestive heart failure. Life expectancy was calculated by a Markov process¹⁰ from age-specific mortality rates adjusted to take account of excess mortality from stroke and/or congestive heart failure.⁶

The probability of a patient experiencing each chance event in the decision tree is affected by each patient's unique clinical characteristics at the time of presentation (e.g., age, the ECG findings, infarct size, blood pressure, etc.). The published literature provides considerable detail on the relative risks for several of these events: the most important ones are the chance of infarction, the chance of death from infarction, and the risk of stroke.⁶ These probabilities have major influence on outcome and must be determined separately for each individual patient. The chance of AMI was determined from presenting ECGs: these were placed into one of six categories (i.e., marked ST elevation with or without reciprocal depression, minimal ST elevation, ST depression, bundle-branch block, left ventricular hypertrophy, and all other changes) that we have previously shown to be associated with different probabilities of AMI ranging from 5.8 to 96.1%.¹¹ The probability of dying from AMI was determined by a predictive instrument developed by Selker *et al.*¹² This instrument predicts the probability of dying from AMI for individual patients, using patient age, pulse rate, blood pressure, and the presence or absence on presenting ECG of Q waves and peaked or inverted T waves (i.e., all information that is immediately available at the bedside). All thrombolytic agents increase the risk of hemorrhagic stroke

FIG. 1 Decision tree for the management of suspected acute myocardial infarction. Only one branch is shown for clarity. The letters A, B, C, and D indicate chance event nodes from which identical branches diverge (i.e., an identical tree follows each of the nodes labeled with the same letter). MI = myocardial infarction, TPA = tissue plasminogen activator.

immediately after their administration. Without thrombolysis, aspirin alone reduces the chance of stroke associated with AMI from 0.8 to 0.4%; only 2.5% of these strokes are hemorrhagic.² The predictive instrument based on the results of Simoons *et al.*⁵ was used to estimate the extra risk of hemorrhagic stroke after thrombolysis. Apart from death from AMI and the chance of stroke, the probabilities of all chance events were derived from data in the MEDLINE medical literature, detailed elsewhere.⁶

The clinical data and ECG findings of 262 consecutive patients admitted to Nenagh Hospital coronary care unit with suspected AMI from January 25, 1993, to October 4, 1994, were prospectively entered into a computerized data base. Acute MI was diagnosed using World Health Organization criteria: chest pain, ECG changes, and creatine kinase at least twice the upper reference limit.¹³ Patient mortality was determined up to 6 weeks after presentation. The predicted outcome for every management decision made for each patient concerning thrombolytic therapy was calculated by the decision analysis model.⁶ These decisions were then compared with those that would have been made had the decision analysis model's recommendations been used, or if a "fast track" triage policy had been implemented. The robustness of the decisions made by decision analysis was also tested by performing repeated decision analyses with varying chance event probabilities and outcome utilities (i.e., quality of life adjustments). This process of sensitivity analyses was used to determine the threshold probabilities and/or utilities at which the preferred treatment option recommended by decision analysis changed.⁷

Statistical comparisons were made using Student's *t*-test and chi-square analysis.

Results

Acute MI was confirmed in 84 of the 262 consecutive patients admitted during the study period. Seventeen (20%) of those with confirmed AMI died within 6 weeks of admission: all of those patients with cardiogenic shock died. Fifty patients were given thrombolytics (47 with and 3 without subsequently confirmed AMI). There was little difference between patients with AMI who were given or not given thrombolysis. Although thrombolized patients presented significantly earlier (4.1 ± 3.6 vs. 8.5 ± 10.8 h, $p < 0.05$), this difference disappeared when the three patients who presented more than 24 h after onset of symptoms were excluded (4.1 ± 3.6 vs. 5.8 ± 5.0 h, $p > 0.05$).

Had therapy been guided by decision analysis, 22 additional patients would have been thrombolized (18 with and 4 without confirmed AMI), and there would have been 3.7 fewer deaths. On the other hand, 0.4 more strokes might have occurred. Without thrombolysis, the total life expectancy predicted by decision analysis for all 262 patients would have been 4,233.3 life years. The predicted total gain from the therapeutic decisions actually made was 28.1 life years, and the predicted total gain from decision analysis-guided manage-

ment was 57.7 life years (Table I). Predicted gains per patient from thrombolysis ranged from -0.6 to $+2.6$ life years; only a few of these gains over aspirin alone were borderline, although several patients were predicted to make only trivial gains from accelerated TPA over streptokinase therapy (Fig. 2).

A "fast track" triage protocol that assumed that only patients with more than 2 mm ST elevation presenting < 6 h after symptom onset would be given thrombolysis, was tested: depending on whether all "fast track" patients were given streptokinase or accelerated TPA, total gains of 35.8 and 52.5 life years were predicted (Table I).

There was no consistent relationship between the predicted life expectancy gain with thrombolysis and the associated increased risk of stroke: several patients with substantial life expectancy gain were estimated to have a low extra hemorrhagic stroke risk, while other patients estimated to have a greatly increased stroke risk were predicted to gain very little life expectancy (Fig. 3). The threshold probability for each chance event, above or below which the decision to give or withhold thrombolysis changed, was usually comfortably distant from estimated probability of the chance event. For example, decision analysis recommended withholding thrombolysis from 19 of the 86 patients with AMI. This decision not to treat would not have changed in 16 of these patients even if the chance of stroke had been zero: of the remaining 3 patients, 1 would have been given TPA had his risk of stroke been $< 0.6\%$, more than half his predicted stroke risk of 1.6% ; the predicted stroke risks of the other two patients were 1.1 and 1.5% , respectively, yet neither would have been given TPA unless their risk of stroke had been $< 0.1\%$.

The quality of life adjustments for both stroke and heart failure had no bearing on any of the treatment decisions: the management of none of the patients would have been changed, even if the quality of life with a stroke and/or heart failure was deemed to be either the same as death or equal to perfect health.

Discussion

This study demonstrates that more patients might benefit from thrombolytic therapy if its administration were directed by a decision analysis model, although this might result in a slightly increased number of strokes. This is not to imply that decision analysis is wiser or better than the bedside clinician. First, the predictions of a decision analysis model are heavily dependent on the probability estimates of MI, death, and stroke. Second, before making a management decision, not only the predicted life expectancy gain but all the other results of the decision analysis must be considered. These other results are provided at the bedside in a computer printout and include explicit estimates of each individual patient's chance of MI, death, and stroke with or without thrombolysis, as well as the threshold probabilities and utilities at which the preferred treatment options change. By providing these different detailed perspectives for each individual clinical decision, our decision analysis model offers a unique advantage of over an-

TABLE 1 Life expectancy, deaths from infarction, and major strokes predicted by decision analysis model for all patients

	n		Life years		Total life years	Years gained over no thrombolysis	Deaths		Total deaths	Extra deaths compared with no thrombolysis	Strokes		Total strokes through
	(n = 84)		(n = 178)										
	MI	No MI	MI	No MI			MI	No MI			MI	No MI	
Then no patients given thrombolytics													
TPA	0	0	0.0	0.0			0.0	0.0			0.00	0.00	
SK	0	0	0.0	0.0			0.0	0.0			0.00	0.00	
No Rx	84	178	707.3	3526.0			21.2	0.0			0.51	0.00	
total			707.3	3526.0	4233.3		21.2	0.0	21.2		0.51	0.00	0.51
treatment actually given													
TPA	3	0	24.4	0.0			0.3	0.0			0.06		
SK	44	3	441.2	62.9			6.5	0.0			0.51	0.00	
No Rx	37	175	270.4	3462.5			11.5	0.0			0.26	0.02	
total			736.0	3525.4	4261.4	28.1	18.3	0.0	18.3	-2.9 deaths	0.83	0.00	0.85
Then preferred treatment option of decision analysis was followed													
TPA	50	5	464.2	55.2			7.4	0.0			0.87	0.08	
SK	15	2	111.2	23.7			4.0	0.0			0.21	0.02	
No Rx	19	171	191.1	3445.6			3.2	0.0			0.08	0.00	
total			766.5	3524.5	4291.0	57.7	14.6	0.0	14.6	-6.6 deaths	1.16	0.10	1.26
Then "fast track" treatment protocol was followed and only SK was given to all thrombolysis-eligible patients													
TPA	0	0	0.0	0.0			0.0	0.0			0.00	0.00	
SK	53	5	468.5	58.6			9.8	0.0			0.71	0.06	
No Rx	31	173	275.6	3466.4			7.2	0.0			0.18	0.00	
total			744.1	3525.0	4269.1	35.8	17.0	0.0	17.0	-4.2 deaths	0.89	0.06	0.95
Then "fast track" treatment protocol was followed and only "accelerated" TPA was given to all thrombolysis-eligible patients													
TPA	53	5	485.4	58.4			8.2	0.0			0.92	0.08	
SK	0	0	0.0	0.0			0.0	0.0			0.00	0.00	
No RX	31	173	275.6	3466.4			7.2	0.0			0.18	0.00	
total			761.0	3524.8	4285.8	52.5	15.4	0.0	15.4	-5.8 deaths	1.10	0.08	1.18

All calculations were made retrospectively, so the probability of infarction was 100% for those with confirmed infarctions and 0% for those without infarction. The probability of death from infarction was determined by the predictive instrument of Selker *et al.*¹²

Abbreviations: n = Number of patients, MI = confirmed myocardial infarction, no MI = no myocardial infarction confirmed, SK = streptokinase, TPA = "accelerated" tissue plasminogen activator, No Rx = no thrombolytic therapy, deaths = deaths from infarction within 6 weeks of admission.

FIG. 2 Life expectancy gains for all 264 patients when treated with streptokinase or "accelerated" TPA regimens. — = Streptokinase, —□— = "accelerated" TPA.

other, recently reported decision support tool.¹⁴ Few physicians would be willing to run a greatly increased risk of stroke to achieve a "mathematically correct" marginal life expectancy benefit. Decision analysis, therefore, is only a guide and can never replace clinical judgment; the final treatment decision must be made by a physician.

The results of any decision analysis depend on the data on which it is based. We believe that the analysis was consistent with the overall thrust of the current literature at the time it was used; future experience may show that the data used were wrong, and that the probabilities of death, major stroke, and so forth, may have to be changed in the light of clinical experience, opinion, and/or better predictive instruments, and so on. The standard ECG has well documented limitations for the early detection of MI: numerous studies have found, as we have done, that about 5% of patients with classical ECG changes do not have AMI, and 5% with AMI present with essentially normal ECGs.¹⁵ Presently we are exploring the relevance and portability of various logistic regression models to estimate the chance of MI in our patient population.¹⁶ Selker et al.'s predictive instrument of infarct mortality (12) was originally validated on 5,773 patients prior to the thrombolytic era and performed well on our, albeit small, number of patients.¹⁷ More recently, a similar, highly accurate instrument has been derived from the results of 41,021 patients studied in the GUSTO-1 trial.¹⁸ Likewise, other instruments for estimating the risk of stroke have become available.¹⁹

There would be no difficulty giving thrombolysis if a substantial life expectancy gain and no increased risk of stroke were likely. We found no consistent relationship between life expectancy gain from thrombolysis and the predicted increased risk of stroke: some patients were predicted to have a substantial life expectancy gain with little increased stroke risk, while others ran a huge increased risk of stroke for only a very small life expectancy gain. Few recommendations of the decision analysis model predicted a marginal benefit, and no two patients were ever the same: the preferred treatment op-

FIG. 3 The life expectancy gain from thrombolysis with streptokinase (SK) predicted by decision analysis with the corresponding extra percentage chance of hemorrhagic stroke for each individual patient estimated by the instrument of Simoons *et al.*⁵ "Accelerated" TPA produced similar results. —□— = Life gained with SK, — = stroke risk.

tion calculated varied from patient to patient according to each individual clinical situation. Decision analysis predictions will be most accurate in clinical situations similar to those reported in the literature. When there is less information available, such as after early or late administration of thrombolytics, or in the treatment of very young or very elderly patients, predictions will be more speculative. Assigning quality adjustments to different outcome states is the most contentious objection to the clinical use of decision analysis.⁷ In actual practice, however, we found that the quality of life adjustments, such as those placed on a major stroke or heart failure, never altered the treatment option preferred by decision analysis. Although no strokes were observed in any of our patients, several of them were either older and/or had higher blood pressure than the average patient of the large clinical trials⁴ and, therefore, had a greater risk of stroke. As it happened, the estimated chance of stroke for the vast majority of our patients was markedly distant from the "threshold" probability of stroke above or below which the decision analysis-preferred management would have changed. Although a "fast track" protocol that treated all patients eligible for thrombolysis with accelerated TPA was predicted to gain almost as many life years as the decision analysis model, decision analysis would have selected several patients for less expensive treatment with streptokinase. Unlike decision analysis, traditional decision making is based on implicit assumptions: if based on knowledge derived from clinical trials, the major assumption is that the patient being treated is comparable with the patients studied by the clinical trial(s). The benefits and risks of thrombolysis for patients encountered in clinical practice may be different from those observed in the large thrombolytic trials, since overall these trials had lower mortality rates than those often observed in our and other coronary care units.²⁰ In real life there is no such thing as an average infarct, as each patient has his or her own individual risk of infarction, death, and stroke. Provided it is based on the best available information, decision analysis will always maximize the efficiency of deci-

sion making, whereas clinicians on their own may apply their knowledge erratically and lose potential benefits for their patients. Decision analysis is particularly well suited to thrombolysis with its urgency, uncertainty, and danger. Moreover, since its decisions are so explicit they can be repeatedly reviewed and analyzed and can be easily defended in the event of a disastrous outcome.

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