Usage Evaluation of Thrombolytics and Adjuvant Therapy Post-MI

Eileen Yoshida, Sandra Gee, Fitzpatrick Obilo and Thomas Einarson

ABSTRACT

Following the publication of the GUSTO study[1] results, our institution developed hospital-specific guidelines for the use of streptokinase (STK) and tissue plasminogen activator (tPA) based on GUSTO subgroup analysis. Additionally, a prospective usage evaluation was initiated to monitor thrombolytic and concomitant post-myocardial infarction (MI) therapy, assess thrombolytic use compared to the guidelines, assess treatment outcome and determine the potential cost avoidance following guideline implementation.

Over a seven-month period, 57 courses of thrombolytics were administered to 56 patients. tPA was used in eighteen cases and with one exception, all patients treated with tPA met the criteria for usage. Ninety-five percent of patients received either enteric-coated acetylsalicylic acid or warfarin post-MI, and intravenous heparin was initiated in all eligible patients. Fifty-two percent of patients received oral beta-blockers. Eight patients died in total; four received STK and four received tPA. Based on a high incidence of hypotension with the bolus method of STK, a continuous rate of infusion for STK was implemented. The results indicated good compliance with the established guidelines and use of adjuvant therapy consistent with the literature. The development of criteria for the use of thrombolytics may have saved our institution up to $150,000 annually in drug acquisition costs.

Key words: *thrombolytics, drug use evaluation*

RÉSUMÉ

Suite à la publication des résultats de l'étude GUSTO[1], et en se fondant sur l'analyse d'un sous-groupe de cette étude, notre établissement a élaboré des lignes directrices sur l'utilisation de la streptokinase (SK) et de l'activateur tissulaire du plasminogène (t-PA). De plus, une évaluation prospective a été amorcée pour suivre l'évolution du traitement thrombolytique et du traitement concomitant en période post-infarctus du myocarde (IM). On a aussi évalué l'utilisation des agents thrombolytiques par rapport aux lignes directrices, les résultats du traitement et calculé les économies potentielles suite à l'implantation de ces lignes directrices.

Au cours d'une période de sept mois, 57 traitements thrombolytiques ont été administrés à 56 patients. Le t-PA a été utilisé chez 18 patients et tous, à l'exception d'un seul, ont satisfait les critères d'utilisation de ce médicament. De l'acide acétylsalicylique entérosoluble ou de la warfarine a été administrée à 95 % des patients après l'IM et de l'héparine a été adminstrée par voie i.v. à tous les patients chez qui elle n'était pas contre-indiquée. Des bêta-bloquants oraux ont aussi été administrés chez 52 % des patients. En tout, huit patients sont décédés; de ceux-ci, quatre avaient reçu de la SK et les quatre autres du t-PA. Étant donné la forte incidence d'hypotension causée par l'administration en bolus de la SK, il a été décidé d'administrer ce médicament par perfusion continue. Les résultats ont montré une bonne adhésion aux lignes directrices mises en place et une utilisation du traitement adjuvant conforme à ce qu'on retrouve dans la documentation. L'élaboration de critères d'utilisation des agents thrombolytiques pourrait avoir entraîné des économies annuelles atteignant 150 000 $ sur le coût d'acquisition des médicaments.

Mots clés : *agent thrombolytique, évaluation de l'utilisation des médicaments*

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INTRODUCTION

In the spring of 1993, the preliminary results of the Global Utilization of Streptokinase and Tissue Plasminogen Activator of Occluded Coronary Arteries (GUSTO)[1] study were announced. This international, prospective, randomized trial evaluated four thrombolytic treatment regimens: (1) streptokinase (STK) with subcutaneous (SC) heparin; (2) STK with intravenous (IV) heparin; (3) tissue plasminogen activator (tPA) with IV heparin; and (4) both STK and tPA with IV heparin. The 30-day, post-myocardial, infarction (MI) data showed a small but statistically significant mortality benefit in the group randomized to receive tPA with IV heparin; however, it was also associated with a higher risk of in-

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hospital stroke. Still, the net clinical benefit in terms of mortality was greatest for tPA with the results suggesting the saving of one additional life per one hundred patients treated with tPA compared to those treated with STK.

Those results which suggested a 1% mortality benefit for tPA over STK generated much discussion regarding whether or not there was sufficient evidence to support the use of tPA as the first-line thrombolytic agent over STK. This recommendation, if accepted, would have had an enormous financial impact on our institution as approximately 110 acute myocardial infarction (AMI) patients are treated annually with thrombolytic therapy. Additional funds approximating $255,000 would have had to have been found if all patients presenting to our Emergency Department were to receive tPA instead of STK.

Following the announcement of the GUSTO trial results, the Pharmacy and Therapeutics Committee and the Division of Cardiology developed guidelines for the administration of thrombolytic agents within our institution in an effort to ensure their rational prescribing. Additionally, a prospective usage evaluation was initiated and performed by the Department of Pharmaceutical Services. The objectives of the evaluation were as follows: (1) to determine the usage patterns and treatment outcome of thrombolytics and post-MI adjuvant therapy; (2) to measure the rate of appropriateness by comparing observed use to the approved hospital guidelines; (3) to make recommendations which may improve the prescribing of thrombolytics and adjuvant therapy, if necessary; and (4) to determine the potential cost avoidance of the implementation of the guidelines. This paper summarizes the results of our study.

METHODS

Our hospital is a 470-bed, acute care, community facility with teaching affiliation. The hospital includes a 14-bed combined medical intensive/coronary care unit (MICU/CCU). After the preliminary results of the GUSTO trial were made public, hospital-specific guidelines were developed in June 1993, for the use of thrombolytic agents within our institution based on GUSTO subgroup analysis. Physicians working in the Emergency Department were inserviced by a Cardiologist and the guidelines were also posted in the Emergency Department. Patients arriving in hospital within four hours of onset of chest pain, who were under 75 years of age and were diagnosed with an anterior AMI (all three criteria had to be met), or patients who had received STK within the previous six months, or had a documented STK allergy, were to receive the GUSTO regimen of accelerated tPA [15 mg bolus followed by 0.75 mg/kg over 30 minutes (to a maximum of 50 mg), then 0.5 mg/kg over 60 minutes (to a maximum of 35 mg); total dose not to exceed 100 mg]. All other AMI patients were to receive STK 750,000 U over 15 minutes then 750,000 U over 45 minutes [total dose 1.5 million units (MU)] i.e., "front-loaded" STK. At our hospital, thrombolytic therapy is routinely initiated via a preprinted order form which includes our institution's approved criteria for thrombolytic usage, as well as orders for adjuvant therapy (heparin, enteric-coated acetylsalicylic acid (ECASA), metoprolol).

During the months of September 1993 through March 1994, inclusive, a thrombolytic therapy usage evaluation was performed by the two MICU/CCU liaison pharmacists (EY,SG). All patients who were admitted to hospital with a diagnosis of AMI and who received thrombolytic therapy were identified during drug order review and monitored prospectively until hospital discharge. The information collected included age/gender of patient, previous use of STK, MI type, duration of chest pain, thrombolytic and dose used, adjuvant therapy, complications and outcome. The study was non-interventional. The use of adjuvant therapy was also evaluated. The existence of concomitant disease states was documented in an attempt to explain why beta-blocker therapy may not have been initiated in a patient. The adverse effects monitored included hypotension, bleeding complications, cerebrovascular accident (CVA), allergic reaction, and reinfarction. Allergies as noted by the physician, nurse, and/or pharmacist in the chart were included. No attempt was made to verify the allergies. The primary outcome measurement of interest was death. At the end of the study period, the data were analyzed.

For study purposes, the following definitions applied. The duration of chest pain prior to thrombolytic administration was defined as the time (in hours) between when patients said they first experienced chest pain (as extracted from the Emergency Department or physicians' notes) to the time the diagnosis of AMI was made. Hypotension was defined as a systolic blood pressure (sbp) less than 90 mmHg and/or implementation of measures to correct hypotension (e.g., Trendelenberg position, fluid resuscitation, inotropic support, temporary or full discontinuation of STK).

Cost avoidance was calculated as follows. Our drug acquisition cost of all thrombolytic agents used during the study period was determined then compared to the cost if tPA had been used in all cases. The difference was then extrapolated to a projected annual sum.

We evaluated the different incidences of adverse outcomes between groups (i.e., STK and tPA patients) using a 2-tailed Fisher's Exact test. A p value ≤ 0.05 was considered significant.

RESULTS

Fifty-seven courses of thrombolytics were administered to 56 patients during the study period. The baseline patient characteristics are displayed in Table I. tPA was used in 18 cases and STK on 39 occasions. One patient who initially received STK reinfarcted and subsequently received tPA. With one exception, all patients treated with tPA during the study period met the criteria for usage as approved by the Pharmacy and Therapeutics Committee (Table II). One patient received tPA, a total dose of 120 mg infused over three hours, which is the regimen currently approved by the Canadian Health Protection Branch. Thirty-eight patients received STK as a front-loaded infusion and one patient was administered STK 1.5 MU as a continuous infusion over one hour. At the time of this study, the drug acquisition cost of STK 1.5 MU was $426.19 and for tPA 100 mg, $2,748.14. The drug acquisition cost of all thrombolytic therapy during the study period was approximately $66,088.

Approximately 95% (53/56) of patients receiving thrombolytics were given ECASA or warfarin post-MI (Table III). Exceptions included two patients who had documented allergies to ASA and one patient who was receiving ECASA prior to admission but for whom ECASA was not restarted in hospital. Intravenous heparin therapy was initiated in all (53/56) patients receiving thrombolytics except for those who died before it could be started. Only 29 of the 56 patients (52%) receiving thrombolytics were ordered oral beta-blocking agents.

Sixteen of the thirty-nine patients (41%) receiving STK became hypotensive during or immediately after the completion of the dose (Table IV). Six of these patients (38%) required discontinuation of the infusion and three died despite resuscitative efforts with multiple inotropes.

Table I: Baseline Patient Characteristics According to Thrombolytic Agent Received

Characteristic	tPA courses (n=18)	STK courses (n=39)
Male/Female	14/4	27/12
Diabetes mellitus	4	3
Asthma/COPD	3	1
Peripheral vascular disease	0	1
Congestive heart failure	0	1
Previous MI	6	10
Inferior MI this admission	1	25
Anterior MI this admission	16	12
Inferior and anterior MI this admission	1	2

* Note: one patient who received STK initially, then reinfarcted and was given tPA two days later, was included under both thrombolytic regimens

Table II: tPA Usage Criteria

Criteria	# Patients Meeting Criteria n=18
Age < 75 years	18
Acute anterior MI	18
Arrival to hospital within four hours of onset of chest pain	17
Documented allergy to STK	0
STK use within six months prior to admission	2*

* In addition to these two patients, two other patients had sustained AMIs within the previous six months but whether they received thrombolytic therapy at that time was not documented.

Table III: Adjuvant Drug Therapy According to Treatment Groups

Treatment	Patients Receiving tPA (n=18)@	(%)	Patients Receiving STK (n=38)	(%)	Total n=56	(%)
enteric coated ASA	11	(61)	35	(92)	46	(82)
warfarin*	5	(28)	2	(5)	7	(13)
IV heparin	18	(100)	35	(92)	53	(95)
beta-blocker	9	(50)	20	(53)	29	(52)
ACE-inhibitor	4	(22)	7	(18)	11	(20)
calcium channel blocker	3	(17)	9	(24)	12	(21)

* patients initially prescribed ECASA but who were changed to warfarin therapy while still in hospital are included in the warfarin group

@ one patient who received both STK and tPA this admission was included in the tPA data only

Table IV: Incidence of Complications and Outcome

Complications/ Outcome	tPA Patients (n=18)	(%)	STK Patients (n=39)	(%)	P Value
Hypotension	0	(0)	16	(41)	0.001
Bleeding (excludes hemorrhagic stroke)	2	(11)	4	(10)	0.812
CVA	1	(6)	0	(0)	0.635
Coronary reinfarction	0	(0)	1	(3)	0.842
Allergic reaction	0	(0)	1	(3)	0.842
Total (Excluding deaths)	**3**	**(17)**	**22**	**(56)**	**0.010**
Death	4	(22)	4	(10)	0.418

The incidence of hypotension associated with STK was statistically greater than that with tPA (p=0.001).

The incidence of all other complications and death was not statistically different between the two treatment groups; however, the incidence of all complications, cumulatively, was significantly greater with the STK treatment group (p=0.010). One patient who received tPA suffered a hemorrhagic stroke. As noted earlier, one patient who initially received STK, reinfarcted and subsequently received tPA. Finally, one patient with no known allergies developed angioedema and hypotension (bp=65/50 mmHg) after receiving half of the prescribed STK dose. A total of eight patients died; four received STK and the remaining four received tPA.

DISCUSSION

Seventeen of the 18 (94%) patients who received tPA during the study period met the hospital-approved criteria for use. One patient did not meet the guidelines because she arrived at the hospital more than four hours after the onset of chest pain. She was a 72 year-old female with a previous AMI in 1987 who, on this admission, was diagnosed with an anterior AMI. She was scheduled for a percutaneous transluminal angioplasty (PTCA) at another institution the following week. Upon consultation with her cardiologist it was decided to treat her with tPA and salvage-PTCA at a subsequent date. Unfortunately, the patient died from cardiogenic shock about four hours after the initiation of tPA.

Of the 39 courses of STK administered, three patients met the criteria for tPA usage but received STK. Two patients under the age of 75 years with diagnoses of anterior AMIs presented less than four hours after the onset of chest pain and received STK. A third patient, aged 49 years, presenting with an anterior AMI approximately four hours after the onset of this episode of chest pain (Note: four to five days prior to admission he was complaining of retrosternal chest pain), received STK. Three days later he reinfarcted due to reocclusion and subsequently received tPA.

The study revealed that a high proportion of our post-MI patients were receiving ECASA or warfarin (95%) and IV heparin (95%) in conjunction with their thrombolytic therapy. The use of such treatments is consistent with the Canadian Consensus Conference on Coronary Thrombolysis (CCCCT) Guidelines[2] regarding adjuvant therapy. Although debate is ongoing regarding the use of STK plus IV heparin versus STK plus SC heparin, our institution continues to use the former strategy. Most data support the use of at least 48 hours of IV heparin in conjunction with tPA to sustain vessel patency.[2-6] The high compliance rate with ECASA or warfarin and IV heparin may in part be attributed to our institution's preprinted thrombolytic therapy protocol which includes ASA 160 mg to be chewed immediately followed by ECASA 325 mg daily. Heparin is routinely initiated six hours after thrombolytic administration.

Also incorporated into the protocol is a section which provides the physician with an opportunity to initiate oral metoprolol therapy. However, in our study only 52% of our patients receiving thrombolytics were prescribed a beta-blocker. This result is consistent with recent literature reports at two other Canadian institutions. Paradiso-Hardy et al[7] reported that 58% of their post-MI patients were prescribed oral beta-blockers. Tsuyuki and coworkers[8] assessed 372 AMI patients who were eligible to receive thrombolytics, ECASA, and beta-blockers. Only 18% and 57% of eligible patients received IV and oral (upon discharge) beta-blockers, respectively. Beta-blockers reduce myocardial oxygen demand secondary to a decline in heart rate, myocardial contractility, and systemic blood pressure, and are associated with limitation of infarct size as well as a reduction in the mortality rate secondary to a decrease in sudden death. Currently, there is still debate as to whether there are any benefits in administering beta-blockers immediately or delaying therapy for up to five or six days post-MI.[9] The CCCCT report strongly recommends indefinite oral beta-blocker therapy which may be preceeded by IV administration when there are no contraindications. The recommendation was based on benefits evident in two large-scale studies.[10,11]

In our study, beta-blockers may not have been prescribed in all cases because of contraindications to their use. Unfortunately, the rationale for withholding therapy was stated in fewer than ten cases. Some documented reasons included sustained hypotension, bradycardia, or heart block. In addition, the existence of concomitant disease states including severe peripheral vascular disease, congestive heart failure, asthma or chronic obstructive pulmonary disorder, or diabetes mellitus may have precluded beta-blockade. In some cases no obvious reason was evident for withholding therapy. Since most recommendations regarding the use of beta-blockers post-MI do not provide specific contraindications, each practitioner must weigh the benefits and risks of treatment in individual patients.

With the exception of hypotension and complications as a whole, the occurrence of adverse events was not statistically different between the two groups. Of note, a 56 year-old female who presented with an anterior AMI and received 84 mg of tPA suffered a major hemorrhagic stroke approximately 12 hours after thrombolysis and died two days later. No patients receiving STK experienced a hemorrhagic stroke. There were no allergic reactions to tPA, but one patient receiving STK developed angioedema which responded to the discontinua-

tion of the infusion and treatment with epinephrine and fluids. He was discharged home with no further chest pain.

Four patients died after receiving STK. The first patient was a 78 year-old female with no prior MI. She suffered a non Q-wave anterior AMI and received STK after more than four hours of chest pain. Her blood pressure dropped from a baseline of 140/80 mmHg to 80/50 mmHg with third degree atrioventricular block after receiving about one million units. She remained very hypotensive despite discontinuation of the STK and administration of inotropes. The patient died approximately two hours after the initiation of thrombolysis. The second patient was a 61 year-old male who presented 12 hours after the onset of chest pain with an inferior AMI. His baseline blood pressure was 130/65 mmHg but dropped to 60/- mmHg after the initiation of STK. The patient died shortly after this incident despite treatment with inotropes. The third patient was a 65 year-old male smoker who had had a previous MI in 1990. He was diagnosed with an inferior AMI after experiencing a sudden onset of retrosternal chest pain unrelieved by sublingual nitroglycerin. Approximately 20 minutes after the initiation of the STK infusion, his blood pressure dropped to 68/- mmHg and was refractory to treatment. The fourth patient was an 81 year-old female with a history of stable angina. After about three hours of chest pain she was admitted with a diagnosis of an anterior AMI. Her blood pressure remained about 112/60 mmHg during the STK infusion. Post thrombolytic administration, she continued to complain of chest pain; occasional, premature, ventricular contractions were noted. Approximately one hour later, she developed asystole and subsequently died.

Four patients died after receiving tPA. The first was a 70 year-old man with a history of non-insulin dependent diabetes, ischemic heart disease, and hypertension who presented to hospital within four hours of onset of chest pain and was diagnosed with an inferior and anterior AMI. Approximately 12 hours after thrombolytic administration he became hypotensive, complained of retrosternal chest pain and went into respiratory failure requiring intubation. Treatment with inotropes was unsuccessful and he developed electromechanical dissociation and died. The next patient was a 68 year-old male with a history of hypertension, angina, previous MI in 1990, and a coronary artery bypass graft (CABG) in1982. He was admitted to hospital in preparation for another CABG, but developed an anterior AMI complicated by cardiogenic shock in hospital. He received tPA but subsequently developed ventricular fibrillation and was transferred to another institution for an emergency cardiac catheterization. He died later after initial stabilization. The other two patients were discussed earlier.

Patients receiving STK experienced significantly more episodes of hypotension (p=0.001) which was also of clinical concern. A review of several large randomized AMI trials reported incidences of hypotension of approximately 6.7-12.5%,[1,12-16] although the rate of the STK infusion as well as the definition of hypotension and use of adjuvant therapy varied among studies. Lew et al[17] reported an 87% incidence of hypotension greater than ten precent of baseline in patients receiving STK 750,000 U over 30±16 minutes for AMI. Based on their findings, the authors recommended a maximum rate of infusion of 500 U/kg/min. in normotensive patients and a slower rate of 200-250 U/kg/min. for patients who are hemodynamically compromised and have a baseline sbp less than 100 mmHg. Based on a body weight of 70 kg, our patients were receiving 714 U/kg/min. during the bolus phase followed by 238 U/kg/min.

An informal survey with pharmacists representing five hospitals in our area revealed that STK was being administered by initial bolus administration followed by a continuous infusion (2/5), or continuously over one hour without a bolus (3/5). Although noted to occur, no specific data were available regarding the incidence or severity of hypotension. At that time, Hoechst-Roussel, the drug manufacturer of STK, was contacted for information regarding dosing recommendations. The bolus method of STK infusion being used at our hospital had been recommended in the 1980s in an attempt to overcome the development of antistreptococcal antibodies. However, since even large doses of STK often cannot overcome the resistance to plasminogen activation resulting from the induction of antibodies and the majority of the thrombolytic trials have used STK 1.5 MU over one hour (no bolus), the company no longer recommends an initial bolus administration. Additionally, we are unaware of any data that suggest greater patency of an infarcted artery with front-loaded STK.

Based on this information, the Department of Pharmaceutical Services recommended that the rate of the STK infusion be changed to 1.5 MU over one hour (no bolus). The cardiologists agreed and the change was approved by the Pharmacy and Therapeutics Committee. We are currently monitoring the effect, if any, of the changes.

The drug acquisition cost of thrombolytic therapy for the 57 courses administered during the seven-month period was approximately $66,088. If tPA had been administered in all cases, the total cost would have been approximately $156,644. Thus, the development of criteria for the use of thrombolytic therapy at our hospital may have saved our institution up to approximately $150,000 annually in drug acquisition costs.

Some limitations are as follows. At our hospital, patients are eligible to receive tPA if the time from the onset

of chest pain to the time a diagnosis of AMI is made is less than four hours. In contrast, the CCCCT Guidelines define the four-hour window from onset of chest pain to actual administration of tPA. However, in our opinion, the time between when a diagnosis of AMI is made to actual drug administration is minimal at our hospital because patients who arrive with possible AMIs are seen immediately, and thrombolytic administration is initiated within ten minutes of diagnosis. Our study was not designed to assess the appropriateness of adjuvant therapy and was non-interventional. Thirdly, our results are dependent on accurate and complete documentation by physicians and nurses. In addition, in assessing the incidence of hypotension we did not consider other potential causes of hypotension including the use of drugs such as nitroglycerin or morphine.

The projected annual drug acquisition cost avoidance of $150,000 is based on the assumption that all patients would have received tPA if the criteria had not been developed and followed by the prescribers. A full pharmacoeconomic analysis determining the cost-effectiveness of each thrombolytic agent was beyond the scope of this paper, but would be beneficial. Finally, similar studies with larger samples of patients who are monitored for longer periods of time should be done.

In summary, an evaluation monitoring the use of thrombolytics and concomitant post-MI therapy and assessing treatment outcome was performed. There was good compliance (94%) with established hospital-specific thrombolytic therapy guidelines and use of adjuvant therapy consistent with the literature. There was a statistically significant greater incidence of hypotension and complications as a whole with STK as compared to tPA. Based on a high incidence of hypotension with the front-loaded method of STK, a continuous rate of administration was implemented. Finally, the development of criteria for the use of thrombolytic agents at our hospital may have saved our institution up to approximately $150,000 annually.

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