Ethic Issue in Ischemic Stroke Patients with Thrombolytic Therapy

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Abstract-

Objective: To discuss the ethical challenge in thrombolytic therapy.

Background: Thrombolytic therapy with recombinant tissue-type plasminogen activator (rt-Pa) has been found to be beneficial to the outcome of patients who had a stroke. However, the ethic issue that is related to intravenous rt-Pa infusion has not been discussed.

Patients: Four patients with a middle cerebral artery (MCA) infarct arrived at the emergency department (ER) of our hospital within 3 hours of stroke onset. All of them violated the guidelines of thrombolytic therapy for patients. The families of three patients insisted on the thrombolytic therapy. Two patients received rt-Pa infusion and two did not.

Results: Two patients who received rt-Pa infusion experienced hemorrhagic transformation. One died on the fifth day after stroke, and the other one had a poor outcome with a modified ranking scale (mRS) of 5. One of the two patients who did not receive rt-Pa infusion suffered from hemorrhagic transformation and died on the third day after stroke, and the other one had a poor outcome with mRS of 5.

Conclusions: These 4 cases highlight the complexity of thrombolytic therapy in patients who violate the guidelines because the families insisted on thrombolytic therapy. No one is sure that the family's decision was the patient's wish. When a stroke patient violates the guidelines of thrombolytic therapy and the family of the patient insists on the thrombolytic therapy, a conversation between patients, patients' families and clinicians is necessary. Physician should tell patient and their families about the high risk of hemorrhagic transformation and mortality. If the family wants to make a decision, physician should request patient or patient's families to sign an against medical advice form and follow the patient's or their family's decision for the outcome.

Key Words: Stroke, Thrombolytic therapy, Ethics, Outcome

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INTRODUCTION

Thrombolytic therapy with intravenous recombinant tissue-type plasminogen activator (rt-Pa) infusion has been shown to be beneficial in ischemic stroke[1]. However, thrombolytic therapy has limitations and a risk of hemor-

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rhagic transformation. Even a stroke patient who arrives at a hospital within one hour of stroke onset, thrombolytic therapy is not always beneficial[2]. Patients have the right to make decision about their health care, including a particular treatment such as thrombolytic therapy. Before they make a decision, they must be able to understand and appreciate the consequence of their action. They must have understood the benefit and the risk of thrombolytic therapy and other treatment options, and they have the right to decide whether they want to receive any treatment[3,4].

In Taiwan, most of the informed consents are made by patient's family. In clinical practice, occasionally stroke patients are brought to ER within 2 hours of the stroke onset, but have one or more conditions that are not suitable for the thrombolytic therapy. According to the guidelines of the Taiwan Stroke Society[5], those patients are not candidate of thrombolytic therapy, but patients' families often against the warning of the neurologist and insist on the thrombolytic therapy for patients. Whether the physician should follow the decision of patients' families or decline their request need further considerations.

PATIENTS

Case 1

A 68-years-old men who had a history of congestive heart failure, diabetes mellitus, hyperlipidemia, atrial fibrillation and myocardial infarction received regular treatments at the Cardiology Department. He did not have a previous history of stroke and he could walk without assistance. He was brought to our ER due to sudden onset of global aphasia and right hemiplegia. Because the interval from stroke onset was over 3 hours, the rt-Pa infusion was not suitable. The brain CT showed hypodense lesions in the territories of left anterior cerebral artery and left middle cerebral artery. He was admitted to ICU under the diagnosis of left MCA occlusion.

At that time, he was alert but had a global aphasia. His systolic blood pressure was 177 mmHg and diastolic blood pressure was 80 mmHg. His heart rate was 74/minute and the body temperature was 36.6°C. His muscle power was 1/5 on the right side and 5/5 on the left side.

His son asked the doctor to give the thrombolytic therapy to the patient even though the neurologist had told him about the risk of hemorrhagic transformation. The reason for the thrombolytic therapy request was that they thought death was better than suffering without hope. Because coffee ground material was found in the nasogastric tube the doctor had refused the thrombolytic therapy. An emergency endoscopy was performed and revealed bleeding in upper body of the stomach, 200 CC coffee ground material was aspirated through the NG tube, and 6 cc Epinephrine spraying was given.

Tranexamic acid infusion and pantoprazole were given for the upper gastrointestinal tract bleeding. Mannitol was given to prevent an increase in the intracranial pressure.

Next morning, the patient's condition was worsened and an emergency brain CT showed a 5 x 4 cm hematoma in the left basal ganglion with rupture into ventricle. There were midline shift to right side transtentorial herniation.

His son transferred the patient to other hospital. The patient died on the third day after the stroke.

Case 2

The case 2 is a 69-year-old man who had a history of diabetes mellitus and hypertension. He had a coronary artery bypass with one vein grafted. He was well and could do daily activity by himself. He did not have a previous history of stroke.

The patient suffered from sudden onset of left limbs weakness, slurred speech and drowsy consciousness. He was brought to ER with Glasgow coma scale of E3V5M6. He had left central type facial palsy, and his muscle power was 2/5 on left side and 5/5 on right side. A brain CT showed widening of cortical sulci, but hematoma or infarct was not observed. His National Institutes of Stroke scale (NIHSS) was 17.

He was considered a candidate for the thrombolytic therapy. However, his systolic blood pressure was 201 mmHg and diastolic blood pressure was 96 mmHg, which were higher than the inclusion criteria for thrombolytic therapy. Anti-hypertensive agent Labetalol was given intravenously, but his high blood pressure persisted.

Because the condition of systolic blood pressure over 185 mmHg and diastolic blood pressure over 100 mmHg persisted, a conservative treatment was suggested. However, the patient's families insisted on thrombolytic therapy for

the patient. Thrombolytic therapy with 0.9 mg/Kg rt-Pa infusion was given and he was admitted to ICU. About 24 hours after the therapy, patient's conditions worsened and the follow up brain CT showed multiple hematomas over both hemispheres, intraventricular hemorrhage and subarachnoid hemorrhage. His coma scale was E2V1M3 and he had a fever. Antibiotics were given for suspected infections. Subsequently, his condition stabilized and he was transferred to a nursing home as requested by his family.

Case 3

The case 3 is a 74-year-old women who did not have a previous history of stroke. She had a history of liver cirrhosis, diabetes mellitus, gastric ulcer and chronic renal disease for many years with regular treatments.

She suffered from a sudden loss of consciousness when she was eating lunch. She arrived at our ER within 1 hour of stroke onset. At ER, her Glasgow coma scale was E2V1M3 with systolic blood pressure of 152/71 mmHg, heart rate of 54/min, and respiratory rate 21. A brain CT showed prominence of the ventricular system and symmetric periventricular white matter suggesting microangiopathic encephalopathies. Liver cirrhosis is one of the exclusion criteria for the thrombolytic therapy, but patient's family insisted on this therapy for the patient, against the neurologist's advice.

Intravenous rt-Pa (0.9 mg/Kg) was given. The brain CT at 24 hours after the thrombolytic therapy showed wedged areas of ischemic infarct in left frontal, temporal and parietal lobes, left basal ganglia and corona radiata with mass effect resulting in mild compression of the ventricle. The patient's condition did not improve. Her conscious level worsened and dyspnea was observed. Endotracheal tube was placed.

On the fourth day, the brain CT showed hemorrhagic transformation in the territory of left MCA with mass effect and uncal herniation. The patient's conditions worsen and she expired on the fifth day after the stroke.

Case 4

The case 4 is a 74-year-old women who had a history of hypertension, coronary artery disease, and atrial fibrillation. She had received regular treatment at the hospital. She was independent in activity of daily living.

She suffered from a sudden loss of consciousness and was brought to our ER within 20 minutes of stroke onset. Intubation was performed soon after her arrival. AT ER, her NIHSS was 32 (Glasgow coma scale E1VEM5, VE: patient with endotracheal tube). Both eyes conjugated to right side. Both pupils had 3 mm diameter and had a prompt light reflex. Her blood pressure was 158/98 mmHg, heart rate 109/min, and her muscle power was 0/5 on the right side and over 3/5 on the left side. An electrocardiography (ECG) showed atrial fibrillation. A brain CT showed a mild edema at right MCA territory. According the guidelines of the Taiwan Stroke Society, the patient's condition was suitable for thrombolytic therapy except NIHSS was over 25.

Because a high NIHSS is associated with a high risk of hemorrhagic transformation, the neurologist explained to the patient's sons and other family members about the risk and the benefit of thrombolytic therapy. The patient's sons had decided that no thrombolytic therapy was to be performed for their mother.

The patient was admitted to ICU and received aspirin and dipyridamol. Mannitol was given for the prevention of increased intracranial pressure. The clinical course was uneventful and extubation was done on the seventh day after the stroke.

However, dyspnea with stridor was observed so intubation was performed again and then a tracheostomy was done. After 14 days treatment, the patient was successful in weaning off the ventilatior. She was transferred to a common ward. The patient was transferred to a nursing home on the twentieth day of the stroke onset. At the time of her discharge, her Glasgow coma scale was E4VTM5 with right hemiplegia and a modified ranking scale of 5.

RESULTS

The demography, stroke type, treatment and outcome were showed in Table. All four patients were not suitable for the thrombolytic therapy. Two patients who received rt-Pa infusion experienced hemorrhagic transformation and one died due to the stroke and hemorrhagic transformation. One of the two patients who did not receive rt-Pa infusion suffered from hemorrhagic transformation and died on the

Table. *Patient demography, treatment and outcome*

Patient	Sex	Age	Stroke type	Stroke score	Family decision	rt-Pa	HT	Outcome
Case 1	male	68	left MCA infarction	NIHSS 25	rt-Pa infusion	no	yes	death
Case 2	male	69	left MCA infarction	NIHSS 17	rt-Pa infusion	yes	yes	mRS 5
Case 3	female	74	left MCA infarction	NIHSS 24	rt-Pa infusion	yes	yes	death
Case 4	female	74	right MCA infarction	NIHSS 32	conservative treatment	no	no	mRS 5

MCA: middle cerebral artery; HT: hemorrhagic transformation; mRS: modified ranking score; rt-Pa: recombinant tissue-type plasminogen activator.

third day after the stroke, and the other one had a poor outcome with the mRS of 5.

DISCUSSION

The four cases reported here highlight the complexity of assessment and management of patients who come to the hospital within 3 hours of stroke onset. Thrombolytic therapy is used for ischemic stroke patients who did not violate the guidelines of the Taiwan Stroke Society. When stroke patients have one or more conditions that violate the guidelines, whether physician should decline the request of the patient or patient's family need further evaluations.

Thrombolytic therapy may cause hemorrhagic transformation. However, hemorrhagic transformation is not always associated with poor outcome or mortality[6]. Even patients do not receive thrombolytic therapy, hemorrhagic transformation is not rare[2]. Violation of guidelines is not always associated with death or significant adverse events[6].

Patients have the right to determine their health care in accordance with a plan that they choose. Autonomy involves the following two conditions: (1) Patient is capable of deliberating about the treatment plan and must be able to examine the alternatives and to distinguish between them. (2) Patient must be capable of putting their plan into action[7]. Besides showing respect for autonomy, physicians should follow the rules of nonmaleficence and beneficience. Physicians have the obligation not to harm patients. It is one of the most traditional ethical principles of medical practice. Beneficience is the positive dimension of nonmaleficence. According to the rule of beneficence, physicians have an obligation to help patients for further interests when they can do this without risk to themselves[3].

The ethical conflicts that resulted from the four cases revolved the following questions. (1) Did those patients really want to receive the thrombolytic therapy? (2) Would the thrombolytic therapy lead to more harm than benefit to those patients? (3) Should we strongly encourage patient's family to accept our recommendation?

About the autonomy, the physician accepted the requests of cases 2, 3 and 4, but they declined the request of case 1. The reason that the physician refused the request from patient's family was because the physician followed the rule of beneficience, that was: thrombolytic therapy for the patient might lead to more risk than benefit. Even thrombolytic therapy was not done, the patient in case 1 suffered from hemorrhagic transformation. Both cases 1 and 4 had poor outcome, when they were discharged from the hospital, and the patient of case 1 died 3 days after the stroke onset. Whether the patient of case 4 would have a better outcome if she received thrombolytic therapy is unknown. Both cases 2 and 3 violated guidelines for thrombolytic therapy, and both of them had poor outcomes. In consideration of autonomy, nonmaleficence and beneficence, when we face a stroke patient with inevitable poor outcome and which violates one or two of thrombolytic treatment guidelines, the physician should tell patient's family about the risk and benefit of thrombolytic therapy and not just to emphasize the risk of hemorrhagic transformation.

According to ethic principles, patient and their families must understand the benefit and risk of thrombolytic therapy and other treatment options, because they have the right to decide whether they want to receive any treatment[3,4]. When we do not tell patient and their families about the benefit of thrombolytic therapy and only emphasis on the

risk of hemorrhage, we violate the principle of self-determination and patient autonomy[7]. Whether the physician should decline the request from patient's family when physician thinks that their decision may lead more risk than benefit to the patient also need to be addressed. According to ethic principles, we must respect patient's decision[3,4]. However, Most patients with left middle cerebral artery infarction have the symptom of aphasia, so they can not understand the risk, benefits and alternative treatment of thrombolytic therapy. Even patients with right middle cerebral artery infarction, may not meet the requirement for informed consent. Because the custom of "substitute decision-making" is not popular in Taiwan, most of the patients do not have surrogate or "proxy" decision maker. When a patient does not have the ability for decision making, most decisions are made by their spouse or adult child. The decision of patient's spouse or adult child is complex. They wish patient's recovery without disability. When physician tells them about the poor prognosis of middle cerebral artery infarction, they may concern about the cost of long-term care, or they may think that death is better than being disabled. Because the decision of thrombolytic therapy must be done within short time, they may make an inappropriate decision. So, when their decision may lead to more harm than benefit to patient, we should do our best to persuade patient or their families to accept our recommendations and not only follow their decisions[8].

It is a highly complex assessment and management for the stroke patients who arrive at ER of the hospital within 3 hours of stroke onset and poor outcome are inevitable. Those patients often violate one or more of the guidelines for the thrombolytic therapy. Maybe thrombolytic therapy is the only opportunity for recovery or for a better outcome. However, because of the high risk of hemorrhagic transformation, most physicians may not agree to perform the thrombolytic therapy. When patient or patient's families insist on thrombolytic therapy when the patient's condition violates the guidelines of thrombolytic therapy, a conversation between patient, patient's families and clinician is the most important. The discussion allows the clinician to mention the high risk of hemorrhagic transformation and mortality. When the family has made a decision, physicians should request patient or patient's families to sign a form (against medical advice form) and follow the patient's or the family's decision to treat the patient[9].

ADDENDUM

The clinical courses of four patients and comments of other experts, had been published in the newsletter of the Taiwan Stroke Society 2009;Vol 6 (2):9-11, and 2009;Vol 6 (3).

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