Review Article

Thrombolysis in elderly patients

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The elderly population consists of those over age 75 years and appears to represent the fastest-growing segment of the population. Intravenous thrombolytic therapy (TT) is the most common strategy for the treatment of acute myocardial infarction (AMI) in many parts of the world. However, TT carries a higher risk of intra-cranial hemorrhage (ICH) in the elderly patients. Primary percutaneous transluminal coronary angioplasty and stenting (PCI) represents an important alternative in these elderly individuals with contraindications to TT. In developing countries, or in areas without availability of primary PCI, TT remains the only therapeutic modality. Dedicated randomized trials are needed to provide a comprehensive understanding of AMI management in the elderly group.

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Key words acute myocardial infarction; thrombolysis; elderly

Introduction

Coronary atherosclerosis is a nearly universal finding in people over age 75 years living in developed countries; however, most of them are asymptomatic. Plaque rupture and thrombus formation play a major role in the genesis of acute coronary occlusion. The introduction of thrombolytic (or fibrinolytic) therapy (TT) was a major advance in the treatment of acute ST-segment elevation myocardial infarction (STEMI). At the end on the last century, the treatment of choice in patients with STEMI was thrombolysis, in the first 12 hours after the event. The proof of efficacy of TT in the treatment of acute myocardial infarction (AMI) comes from 9 randomized placebo-controlled trials. The meta-analysis of these trials showed an overall survival advantage in favor of TT.

The elderly (age > 80 years) represents the fastest-growing segment of the population. Acute coronary syndromes (ACS) are frequent in the elderly and can portend a poor prognosis. Severe coronary artery disease associated with a high incidence of comorbidities with delayed diagnosis and treatments is responsible for the high mortality rates in these elderly patients. Despite the high incidence of STEMI in the elderly, these patients have been excluded from large randomized trials. The reason for under-enrolment of elderly patients in cardiovascular randomized clinical trials (RCTs) remain unclear but it appears that it is likely related to the expected short life span and lack of follow-up in these individuals. In many parts of the world, for patients with STEMI, intravenous TT is the most common strategy. It offers a 26% reduction in mortality compared with conventional treatment, but carries a higher risk of intra-cranial hemorrhage (ICH) than when compared with the younger population.

Primary Percutaneous transluminal coronary angioplasty and stenting (PCI), when performed by an experienced operator, can be an important alternative in elderly patients with: 1) contraindications for TT or 2) management of failed TT or 3) threatened reocclusion in patients with STEMI.

Also, due in part to limited availability of primary PCI, TT remains an important therapeutic modality. Dedicated randomized trials are needed to provide a comprehensive understanding and management of STEMI in the elderly.

About the biological age

It is projected that the elderly population of the world will cross the one billion mark by the year 2020. By that time, over 700 million elderly people will be living in developing countries. It is important that elderly people are not looked upon as a burden to society but rather as an asset. Biological age is a strong determinant of prognosis in patients with AMI. The first question to define is: What is the age limit to be considered an elderly patient? The elderly are best considered as being comprised of several different subpopulations with differing therapeutic goals. Patients who are between the ages of 65 and 70 years can be considered the “young old”. The second group includes those between the ages of 70 and 80 years or “retired old”. In the US, patients >75 years of age constitute 6% of the population, but they represent over half of all deaths after a myocardial infarction. Finally, there are the octogenarians, or the “old old”. At the present time, we are observing a greater demand of ICU admissions for ACS in patients of age >80 years (observational data, non published). It seems also possible to display another profile of the elderly which is the “very elderly” (or very “old old”) patients who are aged >90 years. The Crusade initiative database includes more
than 5,000 ACS patients of this age group, which is one of the largest cohorts of nonagenarians and centenarians ever studied.

Furthermore, the elderly have limited access to medical care in many societies. However, in others, like Spain for instance, there are more than 850,000 citizens aged >85 years (about 1.93% of the total population), and they do not have limited medical assistance because of universal human conditions based on the principle of solidarity of the public health system.

Management of AMI in the elderly patients

The management of elderly patients with acute myocardial infarction (AMI) also appears problematic. Despite the conventional management with aspirin, heparin, platelet aggregation inhibitors, vasodilators, ß-blockers and statins, the morbidity and mortality of the elderly patient group is still high. This is why optimal reperfusion strategy for elderly patients with STEMI remains a hot area of debate. At the end of the last century, the treatment of choice in patients with STEMI was TT in the first 12 hours after the event, mainly in developing countries. The benefit of TT is the greatest when given within the first hours after the onset of symptoms. Any longer delay decreases the amount of myocardial salvage and functional benefit.

In hospitals with cardiac interventional laboratories, primary PCI is preferred if it can be performed by an experienced operator with less than a two hour delay from clinical presentation to the emergency department. Despite evidence from randomized trials that, compared with early TT, PCI after AMI reduces the mortality in middle-aged adults, whether elderly patients with AMI are more likely to benefit from PCI or early TT is not well known until the results of the SENIOR-PAMI trial, which will be discussed below.

Contraindications to TT are prevalent in the elderly, and the incidence of hemorrhagic stroke after TT is strongly associated with age.

Although increasing age is an important risk factor for adverse outcomes among patients with AMI, elderly patients are more often managed conservatively. Beyond their high prevalence in the myocardial infarct population, elderly persons and women fare worse following cardiac events. Gurwitz et al. observed up to 60% of AMI deaths occur in patients aged >75 years.

Clinical trials on thrombolytic therapy

The efficacy of TT in the setting of an AMI has been well established for younger patients by randomized clinical trials. The proof of efficacy of TT for AMI comes from 9 randomized placebo-controlled trials totalling 58,511 patients. The meta-analysis of these trials showed an overall advantage of about 2% (11.5% vs 9.6%) in favor of TT. Clinical trials have demonstrated a consistent benefit from TT in eligible elderly patients with an acute STEMI up to age 75. As a result, the American College of Cardiology/American Heart Association (ACC/AHA) guidelines for the management of AMI strongly endorse TT for patients of age <75 years who present to a hospital within 12 hours of the onset of symptoms of an AMI, with either ST elevation or left bundle branch block (LBBB) without contraindications to TT.

No single randomized clinical trial has evaluated the efficacy of TT in the elderly. However, some clinical trials have suggested a benefit of TT in the elderly. In a subgroup analysis of the ISIS-2 study (Second International Study of Infarct Survival) in 1988, the administration of streptokinase to 1,702 patients aged >70 years resulted in a significant reduction in 35-day vascular mortality. In a similar analysis of 1,215 patients aged >75 years in the GISSI-1 trial (Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto) in 1986, there was a statistically insignificant reduction in 21-day mortality.

In 1994, a collaborative meta-analysis of all randomized clinical trials of more than 1,000 patients raised questions regarding the efficacy of TT among patients aged >75 years. This revealed that the relative effectiveness altered mortality associated with TT, and decreased with the progressive increase of the aged without a know-well reason. Boer et al. in 2002 reported the results of reperfusion therapy in elderly patients with AMI in a randomized study of primary PTCA or TT in patients >75 years of age. This study had a total of 87 patients with an AMI who were age >75 years. Clinical outcome was measured by taking the end points of death and the combination of death, reinfarction or stroke during follow-up, concluding that PTCA had a significant benefit when compared with IV streptokinase for thrombolysis.

Until 2003, no randomized clinical trials have evaluated the efficacy of TT in the elderly. In 2005, the results of the SENIOR-PAMI trial were presented. Patients were recruited from the US and Europe.

Recently, the TRIANA Trial, a randomized interventional treatment of AMI with open label of TT vs primary PCI in elderly patients >75 years of age, is currently recruiting patients with STEMI or LBBB in AMI with <6 hours of evolution without contraindications for TT. This study, verified by the Spanish Society of Cardiology, started in April 2005 and has an expected completion in December 2007. It is hopeful that this study will increase interest in selecting the most viable alternative for older patients with AMI, as to whether this be thrombolysis or intervention.

A new prospective observational cohort study consists of 26,205 consecutive STEMI patients in the Register of Information and Knowledge from the Swedish Heart Intensive Care Admissions (RIKS-HIA), who received reperfusion therapy within 15 hours of symptom onset. This registry compared three arms:
primary PCI (7,084 patients) pre-hospital thrombolysis (PHT) with 3,078 patients in-hospital thrombolysis (IHT) with 16,043 patients.

Results surprisingly demonstrated that primary PTCA was associated with a lower mortality than IHT at 30 days and also correlated with lower mortality than PHT at 30 days. Primary PCI was also associated with a shorter hospital stay and less reinfarction than either PHT or IHT.

Risk of bleeding in the elderly patient receiving thrombolysis

The lack of enthusiasm for TT in the elderly is based on concern about the risk of internal bleeding, especially ICH as well as the clinical evidence that PCI is more beneficial. Other risks are vascular injury at the site of arterial punctures.

Increasing age was the most powerful predictor of hemorrhagic stroke in GUSTO I (The Global Utilization of Streptokinase and tPA for Occluded Arteries), where 60% of the patients who developed ICH subsequently died.

The selection of the appropriate thrombolytic agent

The GUSTO I trial in 1993, demonstrated that cardiovascular outcomes correlates with coronary flow using streptokinase and tPA as thrombolytics. In this study normal coronary blood flow was achieved by 45% of patients aged 65–74, 46% of patients aged 74–85, and 32% of patients age >85 years. This may partially explain the increased rate of re-infarction, congestive heart failure, and shock among patients over age >85, but they do not explain the increased morbidity and mortality in patients aged 65–85 years. The GUSTO-I trial demonstrated a significant survival benefit of tPA over streptokinase, and no other subsequent trial has demonstrated a superior benefit of one thrombolytic agent over another.

Combining thrombolytic agents

After 2001, other clinical trials were designed combining various thrombolytic agents with glycoprotein IIb/IIIa inhibitors. Examples include those such as abciximab with low-doses, reteplase in AMI (SPEED or TIMI-14 investigators), or accelerated tissue-plasminogen activator (tPA) with integrilin in the IMPACT-AMI investigators. Both abciximab and integrilin have demonstrated increased TIMI-3 flows rates when they were compared with either tPA alone or reteplase alone.

In GUSTO IIb, the patients were treated with either reteplase or reteplase combined with abciximab. Among the 2,237 patients aged >75 this combination therapy was associated with an insignificant increase in mortality (18.3% vs 17.9%, P=0.83) when compared with reteplase alone. In the ASSENT-3 study, 6,095 patients were randomized to one of three possible strategies: tenecteplase and unfractionated heparin (UFH), tenecteplase and LMWH, or tenecteplase and abciximab. Despite the reduction in ischemic complications at 30 days after an AMI, the enoxaparin and abciximab group compared favorably to the UFH strategy in that the mortality was similar. In the subgroup of 767 patients aged >75, there was a trend (P=0.11) towards an increased 30-day mortality amongst those patients treated with tenecteplase and abciximab (22.3%) compared with those treated with tenecteplase and unfractionated heparin (15.9%) or tenecteplase and LMWH (15.6%).

Conclusion

TT is feasible for the elderly patients. However, in the treatment of AMI, TT could cause more ICH. PCI is a better alternative to TT, even there was no lower mortality after PCI.

References