ASSENCE

Assessment of cost-effectiveness of Several Strategies of Early diagnosis in patients with acute chest pain and Non Conclusive Electrocardiogram

PRESENTATION OF THE PROTOCOL

The Protocol has been developed at the Santa Maria della Misericordia Hospital, Udine (Italy). It is recognized the need of a clinical protocol to handle patients with acute chest pain without a conclusive electrocardiogram (ECG). The Study Group aimed at assessing which is the best management strategy for these patients. The ASSENCE study is intended to compare accelerated-diagnostic protocol strategies like Dobutamine-Atropine Stress Echocardiography (DASE) and electrocardiographic exercise testing (EET) with the conventional in-hospital observational period. This comparison will be based on cost/effectivenes and quality of life.

BACKGROUND

The Emergency Room evaluation of patients with acute chest pain syndromes and non-diagnostic ECG is a challenge for the physician. Indeed in this time of financial constrains physicians are under pressure to reduce frequency, intensity and, most important, length of hospital stay.

All approaches proposed in the current literature, like computer algorithms, resting two-dimensional echocardiography (Sabia *et al.* 1993), resting perfusion imaging with tallium-201 or technetium-99, try to identify low-risk patients, who could be sent home immediately (Madsen *et al.*, 1988; Varetto *et al.*, 1993; Weissman *et al.* 1996).

It has to be noticed that consequences of inappropriate Emergency Room discharge of patients with acute myocardial ischemia may be serious (Gandhi *et al.* 1995), with up to 8% the patients experiencing myocardial infarction within 48 hours (Geleijnse *et al.*, 1997). Conservative approaches are consequently preferred in common practice, like an observational period in Emergergency or Medical departments. This traditional approach has, however, strong drawbacks, since it provides poor utilization of health care resources. Fifty percent to 60% of Emergency Room chest pain patients are admitted to the hospital after an initial evaluation (Consensus, 1995). Most are found free of cardiac disease during the hospitalization. The average length of stay for these patients is 3 days, and the average hospital costs is estimated close to 6000$ (Graff, 1995)

RATIONALE AND AIM OF THE STUDY

The ASSENCE study is aimed at comparing 3 strategies of handling patients presenting to Emergency Room for unexplained chest pain. The first strategy is based on the current clinical protocol, prescribing an in-hospital observation period and discharge after several hours. The second strategy is based on performing a DASE after 6 hours since chest pain onset and discharging the patient (if DASE is negative) immediately thereafter. The last strategy is based on performing an EET after 6 hours since chest pain onset and discharging the patient (if EET is negative) immediately thereafter. Due to the controversial sensitivity and specificity (Hamm *et al*, 1997, Polanczyk *et al*, 1998), some biochemical markers of myocardial damage like CK-MB and cardiac Troponin will be evaluated as well.

The main goal of the ASSENCE study is to show that an accelerated-diagnostic protocol using aggressive strategies (DASE, EET), which safety has been proved in other studies (Geleijnse *et al.*, 1997) but for which effectiveness only preliminary results exist (Zalenski *et al.*,1997; Colon III PJ *et al.*,1998; Trippi *et al.*, 1997), is more cost-effective than conventional Emergency Department observational period to manage patients presenting to Emergency Room with unexplained chest

pain.. In addition, since medical care intervention must meet a standard of patient acceptability in addition to fulfilling biomedical and physiologic standard, evaluation of patient satisfaction has become an essential element in our protocol. Accordingly, quality of life of the patients will be assessed at admission and at follow up using the NHP Instrument and represents a secondary target of the study.

PROTOCOL

Clinically stable patients presenting to the Emergency Department with unexplained chest pain (no obvious cause), an ECG not diagnostic for ischemia or injury pattern, and normal cardiac enzymes, and who were able to give informed consent will represent our potential study population.. At admission, patient will receive a preenrollment evaluation consisting of history and physical examination, ECG, blood cell count and chemistry, and any further testing deemed necessary by the attending physician. Then, unless a diagnostic end-point will be met (positive cardiac enzyme test result, recurrent chest pain, or new ECG findings consistent with myocardial ischemia) each patient will receive: 1. Repeated cardiac enzyme determination (see below); 2. ECGs (see below); 3. Clinical examination and review of tests results by any attending physician at 0 and/or prerandomization, or for any change in condition; 4. Aspirin; 5. Intravenous line. Nitrates will not routinely be given (unless the patient will develop recurrent chest pain) due to concern for reduced stress test sensitivity (Froelicher, 1989).

After prerandomization clinical examination and tests' review, all enrolled patients will be classified using the following diagnostic criteria:

1. Acute myocardial infarction

   CK-MB mass> 5 ng/ml or

   CK-MB fraction >5% of total CK and/or

   New (40 ms wide) Q waves and a at least 25% decrease in the amplitude of the following R wave or

   New persistent ST elevation of 0.1 mV in ≥2 limb ECG leads or 0.2 mV in 2 contiguous precordial leads

2. Acute cardiac ischemia

   Recurrent chest with any of the following anginal characteristics: pressure with substernal location, radiation to neck, arm or epigastrium, associated dyspnea or diaphoresis, precipitated by exertion or emotion and/or relieved by rest or nitrates

   Development of new ST- or T-wave changes consistent with ischemia : a) ST segment depression of 0.1 mm in ≥2 contiguous leads; b) T wave inversion more negative than isoelectric in ≥ 2 contiguous leads

   New segmental wall motion abnormalities on 2D echocardiography

   Arrhythmia/development of pulmonary edema or cardiogenic shock without evidence of acute myocardial infarction

3. Noncardiac disease requiring urgent admission: aortic dissection, evidence of gastro-intestinal bleeding, cholecystitis, pulmonary embolus, pneumonia, new stroke, active COPD, asthma etc.

4. Patients negative for any of the above and eligible for the protocol

Patients classified in the 4th category will be deemed potential candidates for enrollment.

INCLUSION CRITERIA

1) Acute chest pain within the last 24 hours in absence of local trauma and abnormalities on chest films.

2) A for ischemia non-conclusive admission ECG, CK enzymes and cardiac Troponine-I.

3) Patient able to perform EET

EXCLUSION CRITERIA

1) Age < 30 years.

2) Pre-hospital or Emergency Room complication of acute ischemia or infarct

    Cardiac arrest or ventricular arrhythmya

    Syncope

    Congestive heart failure (bilateral rales above the bases)

    Hypotension (Systolic blood pressure< 100 mm Hg)

3) Protocol performance puts patient at risk

    Premature ventricular contractions > 6/min

    Atrial fibrillation

4) Dilated or hypertrophic cardiomyopathy.

5) Significant (complex) congenital heart disease.

6) Significant valvular heart disease.

7) Known aortic aneurysm > 50 mm.

8) Arterial hypertension > 180/100 mm Hg.

9) Left bundle branch block

Informed Consent Form will be submitted to patients who fulfill inclusion and exclusion criteria . If consent will be given, the Quality of Life of the patients will be assessed using the NHP Questionnaire, and the patient will be randomized to:

1) *Conventional Emergency Department/hospital observational period.* The patient will be hospitalized until a positive or negative diagnosis will be reached timing free according to local protocols.

2) *Accelerated Diagnostic Protocol with DASE* (Dobutamine-atropine stress echocardiography) will be performed[1] within 18 hours since randomization. In patients with a for coronary artery disease positive DASE the diagnosis unstable angina is confirmed, and clinical evaluation will proceed. All patients with negative DASE will be discharged. Patients positive at DASE[2] will be manageg by the cardiologist on the standard clinical protocol.

3) *Accelerated Diagnostic Protocol with Electrocardiographic Exercise Test.* An EET will be performed within 18 hours since randomization. All patients with negative result will be discharged. Patients with positive EET will be managed by the cardiologist on the standard clinical protocol.

After discharge, the patients will be followed up for 2 months by means of telephone calls performed by a registered nurse or physician at 1 week, 1 month and 2 months. The charts of all admitted patients will be reviewed to record dates and times of cardiovascular procedures and complications, and diagnoses. Furthermore, patients who will be admitted, will be called at 2 months after discharge. If telephone contact could not be made, survey sheets will be mailed. The NHP Questionnaire will be mailed to the patients at 2 months

CARDIAC ENZYME DETERMINATION

Blood samples will be taken at admission for determination of cardiac enzymes used for diagnostic purposes (Creatine Kinase MB mass or subfraction, cardiac Troponin). These tests will be repeated 4 hours later. For patients who presented less than 2 hours after the onset of chest pain, these tests will be performed for a third time 6 hours after the onset of pain, so that tests will be performed in all patients at least six hours after onset of pain. Other enzymes may be evaluated as well and reported (Myoglobin, cardiac Troponin I/T, total Creatine Kinase, myosin, ...). Cardiac troponine levels can be determined on either continuous scale or using a bedside rapid test.

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[1] In case of no window at echo, patient will be followed up according to the intention to treat protocol.

[2] Patients resulting positive at basal Echo (according to the criteria specified in the following sections) just before DASE or Exercise testing are considered fully positive (after evaluation by a cardiologist) and treated by the cardiologist according to the diagnosis has been made.

ELECTROCARDIOGRAPHY

A 12 lead ECG will be collected at admission (t=0 hours), before randomization and during each episode of chest pain occurring during in-hospital stay.

DOBUTAMINE-ATROPINE STRESS ECHO TEST

DASE test will be performed within 18 hours since randomization according to the availability of the non invasive laboratory. Only patients with an adequate echocardiographic window at basal echocardiogram (i.e. adequate visualization of at least 13/16 myocardial segments in at least 1 echocardiographic view) will undergo DASE. Dobutamine will be administered intravenously by an infusion pump with an infusion rate of 10 mcg/kg/min for 3 minutes, increasing by 10 mcg/kg/min every 3 minutes up to a maximum of 40 mcg/kg/min. In patients not achieving 85% of their for age and gender predicted maximal heart rate and without symptoms or signs of myocardial ischemia, atropine will be administered, starting with 0.25 mg intravenously and repeated up to a maximum of 1.0 mg within 4 minutes with continuation of dobutamine infusion. Throughout dobutamine infusion the ECG will be continuously monitored and recorded each minute. Blood pressure will be measured and recorded every 3 minutes as well. Reasons for termination of the test will be: horizontal or downsloping ST-segment depression more than 0.2mV at an interval of 80 ms after the J point or ST-segment elevation more than 0.1 mV compared with baseline, severe angina, a symptomatic reduction in systolic blood pressure > 40 mm Hg from baseline, hypertension (blood pressure > 240/120 mm Hg) significant cardiac arrhythmia (ventricular or supraventricular tachycardia) and any serious side effect regarded as being due to dobutamine. A beta-blocker will be available and used to reverse the effects of dobutamine if they won't revert spontaneously and quickly. Every change in wall motion will be recorded. For purposes of analysis, the left ventricle will be divided into the 16-segment model recommended by the American Society of Echocardiography. A normal stress echocardiogram will be defined by a uniform increase in wall motion and systolic wall thickening, with a reduction in end-systolic cavity area. Criteria for interrupting the test were: achieved 85% of maximal heart rate, maximal dose of both dobutamine and atropine, development of new wall motion dyssynergy or by worsening of regional dyssynergy in at least two adiacent segments, horizontal or downsloping ST segment depression ≥ 2.0 mV 80 ms after the J point compared with the baseline, ST segment elevation ≥ 0.1 mV 80 ms after the J point in not Q wave related ECG leads, severe angina, symptomatic reduction in systolic blood pressure > 40 mm Hg from baseline, hypertensione > 240/120 mm Hg, significant ventricular arrhythmias or other severe side effects.

A positive test will be denoted by development of new wall motion dyssynergy or by worsening of regional dyssynergy in at least two adiacent segments. In patients with rest wall motion abnormalities, the biphasic response (i.e., initial improvement of dysynergy ay low dose followed by worsening of dyssynergy at high dose) will be regarded as a positive test.

ELECTROCARDIOGRAPHIC EXERCISE TEST

EET will be performed within 18 hours according to the availability of the non invasive laboratory. The type of protocol used will be determined by the physician performing the test. The EET will be interpreted by the physician performing the test. Criteria for interrupting the test were: horizontal or downsloping ST segment depression ≥ 2.0 mV 80 ms after the J point compared with the baseline, ST segment elevation ≥ 0.1 mV 80 ms after the J point in not Q wave related ECG leads, severe angina, symptomatic reduction in systolic blood pressure > 40 mm Hg from baseline,

hypertensione > 240/120 mm Hg, significant ventricular arrhythmias or other severe side effects.

In presence of a maximal exercise test limited by symptoms (heart rate 220 - age of patient) a ST-change downsloping or linear greater than 1 mm (+80 msec) in two contiguous leads in three consecutive beats, with respect to the resting baseline will be considered a sign of inducible cardiac ischemia.

END-POINTS

1) Length of hospitalization during the index admission, repeat hospitalizations, performed diagnostic procedures and treatments.

2) *In-hospital events*. Coronary angioplasty, coronary bypass surgery, myocardial infarction, cardiac death, cardiogenic shock or cardiac arrest, ventricular tachycardia requiring defibrillation or ventricular fibrillation.

3) *Follow-up events*. Typical angina, re-admission to the hospital for chest pain, re-hospitalization for angina, definite unstable angina, coronary angioplasty, coronary bypass surgery, myocardial infarction, cardiac death.

4) *Quality of life* (psychological well being).

DATA COLLECTION

Clinical data from the Emergency Room evaluation, including the history, results of the physical examination, results of cardiac-enzyme tests, interpretation of the ECG, as well as stress tests results will be recorded by the evaluating physician in the Emergency Room on the standardized Case Report Form that is part of the protocol

STATISTICAL DESIGN

The study is a parallel, three groups randomized trial. The study has been designed for the 2-months re-admission rate taken as primary endpoint of the analysis. The expected rate in the population under study is about 30%. In order to detect an absolute difference of at least 10% between the conventional group and the other two groups combined (corresponding to a relative difference of about 30%) at an alpha-level of 0.05 and a power of 0.80, it is needed to enroll 186 patients in each group (186 vs 372 combined).

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