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Analysis on Cardiac Emergency Treatment and Acute Care

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Abstract – Cardiac-derived stem or progenitor cells have emerged as a possible therapeutic intervention for myocardial infarction, potentially ameliorating the devastating effects caused by inadequate blood flow to the heart. The first human clinical trials using these myocardial-derived cells have recently started, but scientific controversy exists regarding the efficacy and origin of some of these stem cells in preclinical animal models. Systematic review of the current literature on CSCs in ischaemic cardiomyopathy can provide useful additional information on the use of CSCs in pre- clinical trials. By combining all available data, we can adequately compare the different types of cells being used and possibly identify factors that influence cardiac stem cell therapy in general. This protocol provides a thorough description of the methodology that will be used in our systematic review and meta-analysis of all preclinical animal studies involving cardiac stem cell treatment for ischaemic cardiomyopathy.

Keywords: Cardiac Stem Cells, Myocardial Infarction, and Animal Models

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1. INTRODUCTION

In the past 4-5 decades there have been modest advances in our understanding of the disease process. There have been minor changes in the diagnostic criteria and management practices for RF have also largely remained unchanged for the last 20-30 years. However, there have been important changes in the epidemiology both in India and the rest of the world. There appears to have been a sharp decline in RF and RHD in parts of India that have shown improving indices of human development. Physicians living in these parts of India need to be mindful of the prospect of over- diagnosis of RF. For most of India, however, the disease is still quite common and it is important to not miss the initial episode of RF because secondary penicillin prophylaxis still remains the most effective way of preventing RHD.

Acute Coronary syndrome (ACS) has evolved as a useful operational term to refer to clinical symptoms that are compatible with acute myocardial ischemia. Non-ST elevation (NSTE) ACS comprises unstable angina (UA) and NSTE myocardial infarction (NSTEMI). The aim of the treatment in ACS is to prevent myocardial necrosis, fatal or non-fatal myocardial infarction (MI), recurrent hospitalization and resultant morbidity and mortality. The CREATE registry (Xavier *et. al.,* 2008). data revealed that NSTE-ACS patients take a long time (median 420 minutes) to reach to the hospital in India. Surprisingly, the incidence of NSTE ACS patients was less in this registry in contrast to reports from the west where NSTE ACS is more frequent than STEMI. It is important to note that the mortality of STEMI and NSTE ACS is comparable after 6 months (Savonitto *et. al.*, 1999). The adverse events in NSTE ACS continue over days and weeks in contrast to STEMI where most events occur before or shortly after the presentation. A large number of detailed guidelines are available from American College of Cardiology (ACC) / American Heart Association (AHA) (ACC/AHA, 2007) and European Society of Cardiology (Guidelines, 2007). An expert consensus document on the management of ischemic heart disease (IHD) in India is also available (API, 2006). The current document evaluates and summarizes the currently available evidence on the management of NSTE ACS to assist the Indian physicians in selecting the best management.

The term, NSTE-ACS includes UA and NSTEMI. These two conditions are closely related whose pathogenesis and clinical manifestations are similar but of differing severity. The clinical presentation depends on the severity of stenosis and the degree of thrombosis. In patients where ischemia is severe, there can be myocardial damage with the release in troponin I (TnI), troponin T (TnT), or CK-MB and the condition is referred to as NSTEMI. If there is no

evidence of enzyme elevation, the condition is labeled as UA. It is important to remember that the appearance of biomarkers may be delayed by up to several hours after the onset of ischemic symptoms. The distinction between the terms UA or NSTEMI is retrospective. It is also common to describe patients as Trop T- ve NSTE ACS (UA) or Trop T +ve NSTE ACS (NSTEMI).

The typical clinical presentation of NSTE ACS is retrosternal pressure or heaviness ("angina") radiating to the left arm, neck or jaw which may be intermittent (usually lasting several minutes) or persistent. These complaints may be accompanied by other symptoms such as diaphoresis, nausea, abdominal pain, dyspnea, and syncope. There are several atypical symptoms and these include epigastric pain, recent onset indigestion, stabbing chest pain, chest pain with pleuritic symptoms, or increasing dyspnea. Atypical complaints are often observed in younger and older patients, in women, and in patients with diabetes.

Physical examination: The clinical examination is frequently normal. The presence of tachycardia, heart failure or haemodynamic instability must prompt the physician to expedite the diagnosis and treatment of patients. It is important to identify clinical circumstances that may precipitate or exacerbate NSTE- ACS, such as anaemia, infection, fever and metabolic or thyroid disorders. An important goal of physical examination is to exclude non cardiac causes of chest pain and non- ischemic cardiac disorders (e.g. pulmonary embolism, aortic dissection, pericarditis, valvular heart disease) or extra cardiac causes.

Electrocardiogram (ECG): The resting 12 lead ECG is the first diagnostic tool. It should be recorded as soon as possible and immediately interpreted by a qualified physician. The finding of persistent ST elevation suggests STEMI which requires a different treatment. ECG recordings should be repeated at least at 6 and 24 h, and in the case of recurrence of chest pain/symptoms. ECG should be compared with any previously available recordings.

In NSTE ACS, ECG may show ST segment deviation, T wave changes or may remain normal. It should be emphasized that a completely normal ECG does not exclude the possibility of NSTE ACS. In several studies, around 5% patients with normal ECG who were discharged from the emergency department were ultimately found to have acute MI or UA (Rouan *et. al.,* 1989). ST segment shifts and T wave changes are the ECG indicators of unstable CAD. The number of leads showing ST depression and the magnitude of ST depression are indicative of the extent and severity of ischemia and correlate with the prognosis (Holmvang et. al., 2003). ST depression of > 2 mm carries a increased mortality risk. Inverted T waves, especially if marked (greater than or equal to 2mm (0.2 MV) also indicate UA/ NSEMI). Q waves suggesting prior MI indicate a high livelihood of IHD. The utility of ECG becomes less if ECG is abnormal due to pre-existing intraventricular conduction defect or left ventricular hypertrophy (LVH).Ischemia in the left circumflex coronary artery territory is frequently missed in the common 12 lead ECG. It may be detected in lead V4-R, V3- R as well as in leads V7 – V9. These leads should be recorded if clinically indicated.

Biochemical markers: Several biomarkers have been investigated in recent years to be used for diagnosis and risk stratification. Cardiac troponin (CTn) is the biomarker of choice because it is the most sensitive and specific marker of myocardial injury/ necrosis available. Unfortunately, there is a lack of understanding of many of the analytical and clinical issues that govern the use of this important biomarker. The diagnostic cut off for MI using cardiac troponins should be based on the 99thpercentile of levels among healthy controls as recommended by the consensus committee (Thygesen *et. al.,* 2010). All laboratories need to validate their values. The diagnosis of NSTE-ACS should never be made only on the basis of cardiac biomarkers, the elevation should always be interpreted in the context of clinical presentation. Troponin levels usually increase after 3-4 hours. If the first blood sample for CTn is not elevated, a second sample should be obtained after 6-9 h, and sometimes a third sample after 12-24 hours is required. Troponin level may remain elevated upto 2 weeks. Troponin elevation can occur in cardiac and non-cardiac conditions including chronic renal failure. In NSTE ACS, elevated CTn values signal a higher acute risk and an adverse long-term prognosis. The elevated troponin level is also useful for selecting appropriate treatment. Creatine Kinase MB is less sensitive and specific for the diagnosis of NSTE ACS. However, it remains useful for the diagnosis of early infarct extension (reinfections) and peri-procedural MI because of its short half-life.

Many other biochemical markers like CRP, NT- Pro BNP, myoglobin are commercially available. At the present time, there use is not recommended for the diagnosis.

Echocardiography: Echocardiography and Doppler examination should be done to assess the global left ventricular function, any regional wall motion abnormality. Echocardiography also helps in excluding other causes of chest pain.

2. REVIEW OF LITERATURE

Urbanization is occurring rapidly in the Indian sub-continent. Lifestyle changes involving major deviations in diet pattern decreased physical activity due to improved transportation and availability of energy saving devices and high level of mental stress associated with modernization are the important risk factor for coronary heart disease and existing insulin inertia (Ramachandran, 2004).

Favorable risk factors in middle age are associated with lower lifetime risk for cardiovascular disease death and markedly longer survival. These results encourage efforts aimed at preventing development of risk factors in younger individuals to decrease cardiovascular disease mortality and promote longevity (Lioyd-Jones *et al.*, 2006).

Non-modifiable risk factors are those risk factors that an individual cannot change, such as age, gender, ethnicity, and heredity. The incidence of cardiovascular disease increased as people age. Ethnicity and heredity play a role in the development of cardiovascular diseases. Individuals with a family history are at a greater risk for the development of elevated blood lipid levels, which has been associated with the early development of coronary artery disease (Knypl, 2001).

Family history of stroke in any first-degree relative was an independent predictor of ischemic heart disease mortality in men and of stroke mortality in women after controlling for age, cholesterol, blood pressure and diabetes. These results suggest that family history of stroke may be used as a marker for high-risk subjects (Connor and Khaw, 2006).

Modifiable risk factors are those that an individual can change, including elevated serum cholesterol levels, a diet high in saturated fats, obesity, physical inactivity, hypertension, nicotine and alcohol use. Obesity is associated with a higher incidence of mortality from cardiovascular disease and physical inactivity increase the risk for developing cardiovascular diseases.

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2.1 Acute Care & Cardiovascular Emergencies & Card:

Flooding crisis offices and the seriousness of cardiovascular illnesses imply that superior devices are fundamental keeping in mind the end goal to screen patients and send them as fast as conceivable to the most suitable office: concentrated care, clinic affirmations, or release.

The medicinal services challenge

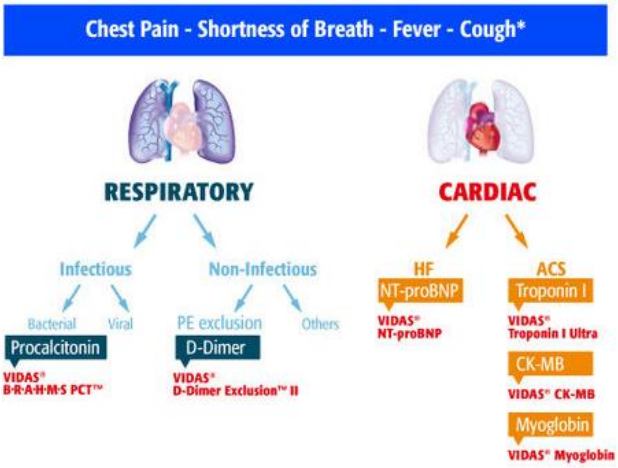
- Cardiovascular illness is the main source of death around the world.
    - 17.3 million Individuals kicked the bucket of cardiovascular ailment in 2008.
- It has a noteworthy effect not just on the life expectancy and personal satisfaction of the people influenced, additionally on medicinal services spending and the economies of these nations.

The part of in vitro diagnostics

In crisis offices, consistently checks. Specialists should rapidly evaluate the seriousness of a sickness and guarantee that patients get the most suitable care immediately. To this end, in vitro symptomatic tests give dependable and fast help.

- The bioMérieux run for crisis divisions incorporates a board of tests for the early analysis of:
    - acute coronary disorder (ACS) and myocardial localized necrosis: troponin I, myoglobin, CK-MB,
    - pulmonary embolism and venous thrombosis: D-Dimer Exclusion,
    - acute heart disappointment: NT-proBNP, Galectin-3,
    - severe bacterial disease/sepsis: procalcitonin (PCT), CRP.
    - This board is reasonable for use on our VIDAS instrument and offers a straightforward, exact and solid answer for encourage proficient

analysis and administration of patients in crisis offices.



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Thromboembolism

This is somewhat known and thought little of ailment that influences 4 million individuals every year in created nations.

- The two essential types of thromboembolism are venous thrombosis, or phlebitis, and pneumonic embolism. In 70% of cases, an aspiratory embolism is brought about by a blood coagulation that relocates from the lower appendages (venous thrombosis) towards the lungs.
    - This is an existence undermining crisis that presents non-particular clinical signs (trunk torment, respiratory inconvenience, and so forth.), making finding troublesome.

Intense coronary disorder

Intense coronary disorder (ACS) is brought about by the blockage of a coronary conduit by athermanous plaque, deterring the basic stream of blood to the cardiovascular muscle. It incorporates myocardial localized necrosis and shaky angina.

- It is characterized by serious agony that begins in the trunk and spreads step by step to the arms and jaw, with a drop in pulse, joined by sweating, queasiness, shortness of breath, and so forth.
- Speed of clinical analysis is vital to guaranteeing that the patient gets mind as fast as conceivable after landing in the crisis division. So as to guarantee the most ideal anticipation, it is suggested that patients get treatment inside 60 minutes: the quick estimation of cardiovascular markers in this manner assumes a fundamental part in patients' survival.
- Of every one of the tests completed, two are deciding elements: the blood troponin test and the electrocardiogram. An echocardiogram and a cardiovascular angioscintigraphy finish the arrangement of tests performed.
- Complementary in vitro indicative tests measure certain substances discharged into the blood when cardiovascular cells are wrecked, for example, troponin, which is thought to be the best organic marker for the finding of myocardial localized necrosis since it is particular to the heart. The blend of different cardiovascular markers and changes to their separate focuses make it conceivable to affirm the determination.
- bioMérieux offers tests to gauge troponin levels and two correlative markers (myoglobin and CK-MB).

3. CORONARY REVASCULARIZATION

The charge of negligence against a cardiologist is very serious one in respect of which the law requires the strict proof of standard of care. Mere allegation that he underwent heart surgery in the hospital, some surgical gauge was left in the site of operation on count of which he sustained severe pain and got removed in another hospital would not be sufficient to sue the cardiologist. There should be cogent medical evidence in support of the allegation that the cardiologist did not render during or post-operative care and treatment, mere pus formation in the stitches after the bypass surgery operation or side effect of the operation or the difference of opinion over diagnosis between two or more group of cardiologists cannot impute negligence.

Revascularization for NSTE ACS is performed to relieve angina, ongoing myocardial ischemia and to prevent progression to MI or death. The indications for revascularization and the preferred approach, PCI or CABGS depend on the extent and severity of the lesions, the patient’s condition and co-morbidity (Guidelines on myocardial revascularization, 2010).

Coronary angiography:

Those patients who have no recurrence of chest pain, normal serial ECGs, no elevation of troponins and no heart failure are considered as low risk. In these patients, a stress test is advised prior to discharge. Coronary angiography is contemplated, if the stress test is positive.

Conservative and Invasive strategy:

There is a controversy, which remains as to the optimal timing between hospital admissions, initiation of medical therapy and invasive evaluation. There are large numbers of randomized controlled trials (RCT), which have addressed this issue. The term invasive strategy refers to coronary angiography and subsequent revascularization within 2 to 24 hours of hospitalization. Conservative strategy (selective invasive) refers to initial medical stabilization followed by angiography and appropriate revascularization, usually within 72 hours or prior to hospital discharge. RCTS have shown that an early invasive strategy reduces ischemic end points mainly by reducing severe recurrent ischemia and the need for re-hospitalization and revascularization (Mehta *et. al.*, 2005). This strategy reduces cardiovascular death and MI at up to 5 years of follow-up (Fox *et. al.*, 2010). From the available data, following conclusions can be drawn.

1. High risk/unstable patients benefit most from the early revascularization therapy & these patients should be promptly treated in advanced centers.

2. A systematic approach of immediate angiography is not necessary in patients who are stabilized with a contemporary pharmacological approach. Likewise, immediate transfer of stabilized patients admitted in hospitals without onsite cardiac catheterization facilities is not mandatory, but should be organized within 72 h.

Percutaneous Coronary Intervention (PCI) and Coronary Artery Bypass Grafting (CABG) :

The mode of revascularization is usually based on the severity and distribution of the CAD. The PCI is usually performed for the culprit lesion-using drug eluting stents. Significant lesions in multiple vessels can be treated either in same sitting or in staged fashion as considered appropriate. CABG is usually advised for complex CAD not amenable to PCI, left main with triple vessel disease, total occlusions and diffuse disease. It is important to consider the bleeding risk as these patients are on aggressive antiplatelet therapy. The benefits of CABG are greatest after several days of stabilization with medical treatment and stopping the antiplatelet agents.

4. RADIOTHERAPY USED IN CARDIAC TREATMENT

Radiotherapy is an essential part of breast-conserving therapy for patients with early stage breast cancer. Randomized trials conducted with a large number of patients have shown that radiotherapy (RT) after breast-conserving surgery significantly reduces local recurrence rate. Furthermore, results of studies with more than 20-year follow-up have proven that lumpectomy with adjuvant whole breast RT for patients with early stage breast cancer equals to mastectomy by local recurrence rate and overall survival.

Recent meta-analysis of data of trials performed worldwide has shown that RT after breast-conserving surgery significantly increases patient survival (5). Study by Buchholz et al. demonstrated that for clinical stage II breast cancer, breast-conserving surgery with following RT provides statistically significant increase in survival, comparing to mastectomy without radiotherapy. Recently, Vicini et al. demonstrated that some distant metastases could directly develop from recurrence in ipsilateral breast, so sup- porting the importance of local tumor control in the overall treatment of patients with breast cancer. Standard RT method after breast-conserving surgery is whole remaining breast irradiation with two tangential fields (regional lymph nodes are irradiated according to indications). During whole breast irradiation, normal organs, such as lung and, in the case of left breast irradiation, heart, are unavoidably included in high-dose region, and so serious radio- therapy damage to these organs can occur. Early toxicity occurs mostly in skin tissue, but radiation dose does not induce heavy damage to skin, and such acute reactions are transient and clinically insignificant. Late reactions, developing in healthy lung and heart tissue included in tangential fields, are clinically significant. Most significant heart RT complications are related to myocardium damage and are generally responsible for the excessive cardiac mortality in patients with breast cancer after radio- therapy. According to Gagliardi et al., excessive cardiac mortality in patients with breast cancer after whole breast irradiation with a prescribed dose of 50 Gy is 12% from myocardium damage and 9% from radiation damage of other heart structures. Multiple studies proved that probability of development of late complications in heart and lung as well as grade of complications is correlated with relative organ volume, which receives clinically relevant dose.

Clinical results of RT should be always balanced with probable acute and late radiotherapy complications. In order to reduce probability of the development of late complications, various modern RT technologies allowing sparing of normal tissues are introduced in clinical practice.

According to data by Muren et al., significant heart and lung complication reduction is achieved using three-dimensional conformal radiotherapy (3D-CRT), comparing with two-dimensional conventional RT. However, even nowadays with wide use of 3D- CRT,

excess cardiac mortality still persists in patients with breast cancer, receiving postoperative RT courses, as compared to normal age-matched female population.

CONCLUSION

Patients with NSTE ACS after the initial phase carry a high risk of recurrence of ischemic events. Therefore, active secondary prevention is an essential element of long-term management. Life style alterations are very important. This is termed as therapeutic life style changes (TLC). Smoking cessation, weight reduction, blood pressure control, management of diabetes, lipid intervention, antiplatelet agents, beta blockers, ACE inhibitors (or ARB) remain extremely important interventions. Isotonic exercise like brisk walk, swimming, cycling, jogging for 30-45 minutes daily or at least 150 minutes weekly should be advised to all these patients. The exercise prescription (type, duration and intensity) should be individualized based on the clinical status of the patient. Lastly psychological factors like anxiety and depression are to be identified and treated (Joep *et. al.*, (2012). Mean probability of excessive cardiac mortality was reduced by use of respiratory-gated radiotherapy by 82% as compared with the control group and by 75% as compared with free breathing plan of the same patient. Mean probability of lung pneumonitis was reduced by use of respiratory-gated therapy by 53% as compared with the control group, and by 59% as compared with free breathing plan of the same patient. This is especially important from point of view of heart complication probability, as excessive cardiac mortality remains one of the important issues of postoperative breast irradiation in patients with early-stage breast cancer.

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