

Autologous Mononuclear Fraction (Stemcells in Lay Man Term) For Dilated Cardiomyopathy

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ABSTRACT

Dilated cardiomyopathy is a type of heart muscle disease that causes the heart Ventricles in lay man word Ventricles means chambers to thin and stretch which grows larger. It typically starts in the hearts left ventricle. Dilated cardiomyopathy makes Unpliable for the heart to pump blood to the rest of the body if untreated which leads to heart failure. Generally the treatment includes ACE inhibitors ;ARB; Diuretics; Beta Blockers; Digoxin etc. Some times the Patient doesnot get response to maximum medical management options then Heart transplantation which is very costly affair and it takes lot of time to get discarded heart .Then the better option is to transplant autologous Bone marrow mononuclear fraction into caronary artery /injecting into cardiac muscle helps to increase in Left Ventricular ejection fraction drastically ;Improves Newyork heart association functional classification score

Keywords: Autologous; Mononuclear fraction; Left Ventricular ejection fraction; Heartfailure

INTRODUCTION

cardiomyopathy is defined as disease of heart muscle. It causes heart to have a harder time in Pumping the blood to the rest of the body which can lead to symptoms of heart failure. It is an acquired or hereditary disease of heart muscle. Symptoms include Shortness of Breath; edematous legs; Abdominal Bloating; edematous feet etc. Some Patients never express any symptoms. As cardiomyopathy Progresses the heart becomes weak and couldnot maintain normal electrical rhythm which can lead to heart failure and arrhythmias which were called irregular heart beat in lay man term .Dilated cardiomyopathy; Hypertrophic cardiomyopathy; Restrictive cardiomyopathy; Left Ventricular Non compaction Cardiomyopathy; Arrhythmogenic non ventricular dysplasia are the different types of Cardiomyopathy.

This paper focuses on autologous mononuclear cell transplantation to Dilated cardiomyopathy when medical therapy fails for some patients suffering with Dilated Cardiomyopathy. The option is only Heart transplantation as it is very difficult to get deceased heart and it also Post Operative immunosuppression is needed which is again challenging with lot of chances of mortality . Autologous bone marrow derived mononuclear fraction which possess the Stemcells is one of the promising treatment for Dilated cardiomyopathy when medical treatment fails

Aims & Objectives:

1. To improve LVEF in Dilated cardiomyopathy Patients

2. To improve Newyork Heart Association score in Dilated cardiomyopathy Patients.
3. To reduce Mortality in Dialated Cardiomyopathy Patients

Research Methodology: Dialated Cardiomyopathy is a condition in which the left ventricle is dialated. As the left Ventricle gets larger it's thick muscular wall stretches and gets thinned out and weak which affects hearts ability to pump enough oxygen rich blood to rest of the body which can lead to heart valve problems; Arrhythmias; blood clots in heart; cardiac failure followed by cardiac arrest. One third of the DCM Patients is hereditary. and other etiology includes

1. Autoimmune conditions
2. Viral infections like retroviral infection; Hepatitis infection
3. DM Type -2;
4. High BP
5. Thyroid Disease
6. Post Partum complications
7. Coronary Heart disease
8. Heart attack
9. Complications during Antinatal Period
10. Complications during delivery
11. Exposure to toxins such as alcohol; illegal Drugs; Certain cancer treatment

The following are the symptoms of cardiomyopathy

1. Fatigue
2. Pain in chest
3. Edematous legs and ankles and abdomen
4. Palpitations
5. Murmur in the heart
6. Trouble breathing due to accumulation of fluid in the Lungs

Diagnosis of cardiomyopathy includes Taking detailed medical history from Patient followed by Physical examination and auscultation. Haematological investigations to rule out autoimmune conditions and to measure the level of haemoglobin and serological investigations such as Viral marker tests for RetroVirus and Hepatitis should be done (ELISA which is gold standard investigation and Immunochromatography tests such as Rapid tests are highly preferred); Hormone assays such as Triiodothyronine; Total Thyroxine; Thyroid stimulating hormone can be done. Caronary angiography should be performed which screens caronary arteries to look for the disease. Cardiac catheterisation to measure Pressure in and around the heart. ECG to be Perfomed to detect abnormal rhythms. 2D Echocardiography should be performed and it is the most important test to know about structures of heart. Electro Physiology study to be performed to measure electrical activity to assess the risk of sudden mortality. Holtermonitoring should be done to measure the electrical activity of heart in the daily routine .Thread mill test should be done to measure heart function when the Patient runs and walks on the thread mill and other imaging modalities like caronary CT; Coronari MRI; Nuclear Heart scan and MUGA should be considered .Genetic evaluation including Genetic counseling should be considered to look for Variants that cause DCM and counseling to understand the process what it might have mean for the Patient and the family of the Patient

The current Pharmacological therapy includes

1. ACE Inhibitors
2. ARB
3. Beta Blockers
4. Anti arrhythmia drugs 4.SGLT2 inhibitors
5. Anticoagulants
6. Aldosterone antagonists
7. Diuretics
8. Neprilysin inhibitors. Surgical modalities include Heart transplantation from deceased donors as it is very difficult to get a deceased donor as it is time consuming and as it is Very expensive .If it is done also post operatively strict immunosupression should be maintained and mortality rate is very high with Heart transplantation as the HLA matching will be not done to deceased donor and the erecipient especially in Cardiac Transplantation. So an alternative to this is autologous bone marrow mononuclear cell transplantation in lay words it is called stemcell transplantation is Preferable.

Stemcells are the unspecialised cells with a capacity of transforming into other mature cell types. Self renewal and Assymetric division are the Primary Properties of stemcells. Progenitor cell is the step between the stemcell and Specialised cell. The Progenitor cell has nil properties of self renewal but it differentiates into specialised cells. There are Totipotent stemcells; Pluripotent stemcells; Unipotent; oligopotent and multipotent stemcells.

A stemcell which can give rise to all the three germ layers as well as to embryo is defined as Totipotent Stemcell. A stemcell which can give differentiate along single cell line is called Unipotent stemcell. A stemcell which has capacity to develop into few cells is called Oligopotent stemcell. A stemcell which can give rise to all three germ layers but it cannot give rise to cells of embryo and Placenta is called Pluripotent stemcells. Multipotent Stemcells are the cells that can be differentiated into multiple but limited number of cell lines

We are going to discuss about the Haematopoietic stemcells which comes under the category of Multipotent stemcells. The Epigenetics of stemcells Play a important role in stemcell regulation such as Modification of histones.; Transcription of DNA; variable gene expression; remodelling of chromatin structure. Addition of methyl group to DNA which turns the gene off is the common method of epigenetic regulation. Identification of stemcells can be made by having a Particular Cluster of Differentiation marker CD+ but never CD-which are the cell surface molecules that consists of genes with specificity and their Protein Products and follow their maturation and Plasticity.

HSC are CD34+; CD90+; CD59+ and MSC are CD70+, CD90+, CD105 +. These Haematopoietic stemcells are Present in Peripheral Blood as well as Bone marrow etc. Bone marrow stemcell niches are endosteal and Perivascular. The bone marrow contains Nucleated red cells; Non nucleated red cells; Monocyte; Multilobed nuclear cells as well as Hematopoietic stemcells and Mesenchymal stemcells where as Monocytes and lymphocytes are regarded as Mononuclear cells. These Mononuclear cells. The autologous mononuclear fraction especially monocytes should be picked up with out Picking up the monocytes. The scientist who has been a doctorate or post doctoral degree holder in BioTech/Medical BioTech; and regenerative medicine/regenerative science scientists should pick up monocytes from Mononuclear fraction and Also HSc as these qualified People will be well trained in Bio Analytical techniques. Neutrophils are Proinflammatory as well as Neutrophils Promote Metastasis if there is any hidden malignancy. Formation of Premetastatic niche by awaking dormant cancer cells at distant site. Epithelial Mesenchymal transition decreases cell adhesion and aiding tumor cells in migrating from tumor site. So neutrophil contamination should be avoided strictly. Lymphocytes mediated response Perpetuates chronic inflammatory responses which are dangerous to human health. Lymphocytes contribute to the spread of cancer cells by enhancing tumor cell motility; invasion; Angiogenesis; Lymphangiogenesis and remodelling of extra cellular matrix. Metastatic colonisation Promoted by B - Cells triggers Pathogenic immunogenicity responses by recruiting immune suppressive cells. B-Lymphocytes in addition to metastatic Property can exhibit anti metastatic properties thus Playing a dual role. So neutrophils; Lymphocytes should be avoided during the retrieval of mononuclear fraction even lymphocytes which belong to mononuclear fraction.

The monocytes which is a Progenitor cell that give rise to diverse cell types which can be generated via common myeloid Progenitor and monocytes Progenitor into hematopoietic Stemcells which represents monoblasts Precursor Population which are earliest form to become Monocytes. The monocytes mature into tissue resident macrophages; Langerhan cells of skin; kupffer cells; Microglia; endothelial cells; dendritic cells; osteoclasts etc. When appropriately stimulated these Monocytes migrate to site of inflammation; extravasate to tissues from circulation acquiring the characteristic features of activated macrophages which involves inflammatory cytokines release; anti microbial oxidative radicles Production; tissue debriefing Proteinases Production and elevated Phagocytic activity noticed in acute inflammatory Phase. Once the inflammatory debris is cleared the macrophages will contribute to wound resolution thus promoting angiogenesis; matrix Production and cell Proliferation. This triggers anti inflammatory and regeneration capability. The Phagocytosis of apoptosis cells initiates Phenotype Promotion which is regulated by various metabolites; functional proteins such as hormones and tissue derived cytokines.

The Doctoral degree holders /Higher doctoral degree holders in BioTech/Medical BioTech and regenerative medicine /regenerative science professionals who is holding regenerative medicine /regenerative science should retrieve the mononuclear fraction especially monocytes with out contamination under strict aseptic conditions. These monocytes which are a part of mononuclear fraction should be handovered to cardiologist in sterile environment and the cardiologist will transplant the stemcells into the patient coronary arteries through canula ting radial or femoral arteries of the Patient. After injecting the mononuclear fraction especially monocytes into coronary artery then the Autologous PRP should be retrieved from the Patient peripheral blood and the retrieved PRP should be injected into the patient coronary arteries as the alpha granules in PRP possess the stemcell differentiation Property; Stemcell Proliferation Property; Stemcell adhesion Property; stemcell homing Property and maintaining stemness Property. Granulocyte colony stimulating factor injections which are injected subcutaneously. PRP also should be retrieved manually by expert scientist so that they ensure PTP optimisation techniques such as four degree centigrade incubation for thirty minutes is required to achieve elevation in alpha granule release which is defined as Temperature Preconditioning and Dilution optimisation techniques such as saline dilution to twenty five Percent lowers anti angiogenic potential which is called Dilution optimisation technique. we recommend the manual retrieval of autologous mononuclear fraction (Stemcell in Layman term) and autologous PRP also by scientist to ensure that the anticoagulant and density gradient varies and the sample quantity and the remains techniques and their management mathematical calculations in retrieving autologous mononuclear fraction especially monocyte. and autologous PRP varies from Patient to Patient based on ailment ;complete blood counts including Peripheral smear examination by Pathologist ;Coagulation Profile; age and weight of the Patient. As Per the United States Federal Drug Administration states that Rinsing; sizing;

cleaning; Examples; Density gradient separation; Centrifugation and cell selection and also under the same surgical sitting requirements the United States Federal Drug Administration rules 361 HCT/P includes same Patient ;Same facility; single Procedure; cells or tissues may be completely rinsed; cleaned; temporarily Stored so that HCT/Ps remain in the original form.

RESULTS AND CONCLUSION

We have followed patient after procedure for 6months duration regularly as the cardiologist injected the autologous mononuclear fraction especially monocytes and autologous PRP to the patient with 45years Male with EF 16 percent with NHYA score 4 not responded through maximised medical management after 4th month of Autologous mononuclear cell transplantation in layman term called stemcell transplantation the Patient LVEF improved to 36.5 percent and his NHYA score improved to class 2 as previously Pre procedural approach was he used to get admitted twice in a month for the worsening of symptoms and used to get dobutamine injection and Diuretic injections and from the second month Post Procedure he started coming to review only once in a month to OPD when the cardiologist suggested the date for review as he said his symptoms started improving and Prior to Procedure the patient is having heart failure (DCMP) from 7 years he is using SGLT2 inhibitors from 6years; Digoxin; HMG Co A reductase inhibitors; dual anti platelet drugs and diuretics orally with large dosage and now he is on these drugs with mild dosage. As this Autologous mono nuclear cells(Stemcells in lay man term) helped to alleviate the symptoms of DCMP and also resulted in drastically increase in LVEF in this middle aged male person which suggests that previously which when he used maximum medical management that doesnot result in improvement of NHYA score and also decreased LVEF for 6years but after the autologous mononuclear cell (stemcell in layman term) transplant have improved in NHYA score and also resulted in increase in LVEF from the second month itself continued the same EF till 5months and waiting to see patient on review on this month (6th month) .The Text book Braunwalds Heart disease which is followed by many cardiologists world wide mentions cardiovascular regeneration and tissue engineering.

This Paper suggests that Autologous mononuclear cell therapy (Lay man term Stemcells) may be considered as treatment option for those patients with worsened symptoms and low LVEF when not achieved through maximum medical management to improve their survival rate and to improve symptoms as heart transplantation is costly affair and not easily accessible.

We took Institutional Ethics committee approval as Per the order issued by Government of India; Ministry of Health and family welfare (Department of Health research) Dated 3.3.2024 signed by Undersecretary; Government of India on 3-4-24 Vide T.11016/02/2023-HR

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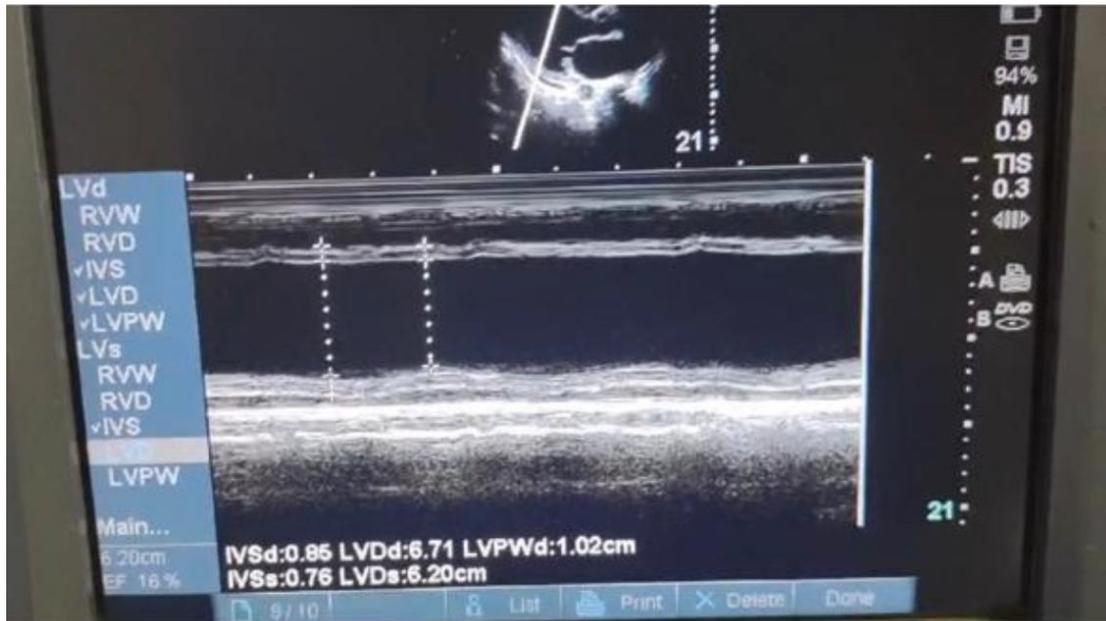
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Pre Procedure 2D Echo



Post procedure echo after 5months

