ejpmr, 2016,3(5), 635-641

SJIF Impact Factor 3.628

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

SCOPE OF NANOMEDICINES AGAINST CORONARY ARTERY DISEASE: A REVIEW

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Article Received on 29/03/2016 **Article Revised on 19/04/2016** **Article Accepted on 01/05/2016**

ABSTRACT

Coronary artery disease (CAD) is a very composite chronic heart disease which leading to cause of death and impairment global.CAD is mainly happened due to genetic and environmental factors, the effects of which are mainly interceded through cardiovascular risk factor.CAD is generally associated when the major blood vessels which supply blood,oxygen and other nutrient to heart become damaged. Cholesterol containing plaque in arteries and inflammation are also the main reason for CAD. Healthy arteries have some elastic fibers that are like rubber bands in the tissue that are allow to expansion and recoil during blood flow, In most of the cardiovascular diseases, elastic fibers in arteries get damaged, which creating hooks that can be used to target drugs. Surgical treatment is one of the oldest method of management of these diseases. But these techniques can lead to additional morbidity in that they provoke central nervous system disturbances, as well as gastrointestinal complications in few patients.The application of nanoscience in relation to heart diseases which provides some technology to design and develop newer cardiac instruments, which are not only smaller in size but also more effective, the nanoparticles, coated with a sticky protein, which attached onto damaged arteries and can deliver a drug to the site in slow release mood and can deliver an array of drugs to the damaged or clogged artery. The main aim of this review is to provide a general overview of the potential benefits of nanotechnology in coronary artery disease..

KEY WORDS: Coronary artery disease,management of CAD, nanomedicine,

INTRODUCTION

Coronary artery disease(CAD) is one of the most dangerous conducting causes of adult deadlines in present days,it is occurred due to atherosclerosis. A disease with complex chronic inflammatory disease,it is mainly characterized by renovation and narrowing of the coronary arteries which mainly supplying oxygen,blood and other nutrient to the heart. the main cause of CAD is atherosclerosis, it is the accumulation of lipoproteins within blood arteries walls. It is mainly a systemic inflammatory processes[1]. Nanomedicine will now provide a new corresponding ways to treat "coronary artery disease" (CAD) which is now one of the most global problem, According to the NIH and American Heart Association(AHA) statistics, near about 80 million people in the U.S. suffer from this CAD and more than 35% of American deaths occurred due to coronary disease.[2] The last innovative technology to influence on cardiocascular disease occurred over a long period ago with the introduction of the coronary stent by Palmaz & Schatz FDA approved in 1994.[3] Since then, emergency management with drugs has relied upon CAD like some, statins, beta blockers, diuretics,antidiabetic drug and surgical procedures such as Coronary angioplasty and implantation of coronary stents, coronary artery bypass grafts and stenting to treat CAD.[4] The new technology for early detection and treatment for coronary artery disease are limited.In recent developments of nanomedicine has become played an important impact on coronary artery disease and there treatment by improving therapy and diagnosis.[5]

Nanomedicine can provide a variety of delivery systems for drugs and genes that can created many problems within the arteries. In relation to coronary artery disease and its sequelae, nanomedicine has become an important tool to detect and treatment of some of the leading causes in the developed world, including atherosclerosis, thrombosis, and myocardial infarction.[6] In order to developed the current status of these disease, nanotechnology provides variety of nanomaterial coatings, in order to controlled-release nanocarriers, to prevent blocked artery. Nanomedicine could increase the efficiency of drugs by improving local and systematic delivery to atherosclerotic plaques or atheromas and reduce the inflammatory response after intravascular intervention.[7]

Therefore, control of Coronary artery disease in present day is utmost important because it is widespread problem and this problem has a severe effects on heart health and it causes potentially fatal complications such stable angina, acute coronary syndrome, heart attacks and sudden cardiac death.

1. Coronary artery disease (CAD)

The basis pathology involved in CAD is atherosclerosis, a complax incitive process which implying the arterial wall. It is mainly occurred due to the accumulation of low density lipoprotein (LDL) in the arterial wall and this deposition subsequently alter into foam cells lead to atherosclerotic plaque. These deposition are simply called atheromas and they cause a thickening of the arterial wall and a narrowing of the arterial space through which blood are supply to the heart.[8] The amount of blood reaching and supplying the heart (myocardium) with oxygen and nutrients can therefore be reduced in the presence of atheromas. An atheroma usually begins to develop as a consequence of impairment or injury to the inner lining of the artery called the endothelium. As the deposits on the plaques grow in size the blood vessels become further more narrowed and there may be obstruction leading to a heart attack or a myocardial infarction.[9] Clinical symptoms associated with this chronic advance are mainly due to the oxygen supply–involve mismatch to the organs affected by restricted blood circulation.

1.1 Major complications associated with CAD

Mainly angina pectoris and myocardial infarction are the most severe complications associated with Coronary artery disease. Angina pectoris is one of the complicated forms of cardiovascular disease, which occurred predominantly when heart is not getting enough blood. Blood carries the oxygen and nutrients to the heart, which is very important to keep pumping the heart, due to the deposition of plaques on lining of the artery it can cause narrow of artery which leads to less supply of blood to the heart, when the heart does not get enough blood, it can no longer function at its full capacity. Prolong or unchecked angina can lead to a heart attact or increase the risk of having a heart rhythm abnormality either of these can cause sudden death of patient.[10] Similarly myocardial infraction is also a medical emergency due to ischaemic necrosis of the myocardium (heart muscle) .A severe blockage in coronary artery leading to great reduction in the blood supply to the heart is most common cause. If the blood supply is cut for few minutes, myocardial cell died and cause infarction of myocardial cell.[11]

1.2 Main factors of coronary artery disease

There are many more factor which raise a risk of CAD and its often cause a life threathining complications like hypertension, diabetes, dyslipidemia, and obesity are some of genetic disorder which leads to cause a complications of heart and some lifestyle factors such as smoking, an unhealthful diet and inertia can increase the risk of coronary artery disease and its complications.[12]

So, therefore management of with coronary artery disease is very important to reduced the complications associated with these factors.

1.3 Management of CAD

For the control of risk factor associated the CAD involves generally;

1.3.1Emergency management of this disease with drug which lower the minimum level of risk like hypertensions, diabetes, dyslipidemia etc.[13]

- Various drugs are available for management of high cholesterol such as atorvastatin, pravastatin and simvastatin.
- Blood pressure lowering drugs available include: atenolol and metoprolol, amlodipine enalapril and captopril losartan and, diuretics such as hydrochlorothiazide
- Drugs that can be used to control blood sugar include: Insulin, Metformin, Sulphonylureas like glimepiride and gliclazide, Thiazolidinediones such as pioglitazone.
- For control of angina, nitrates can be used.

1.3.2. Coronary surgery and nidation of coronary stents

Coronary angioplasty and coronary stent placement is also called percutaneous coronary revascularization it is also a medical procedure where, a long thin tube is blew over into the infected part of the artery and a punctured balloon placed in the constricting. This balloon is then expanded, which buttons fatty depositions or plaques against the artery walls. A stent or thin piece of mesh is left in position to keep the artery open.[14]

1.3.3 Coronary artery bypass surgery

Open-heart surgery or bypass surgery is oldest method of treatment of these diseases. But these techniques can lead to some problem like they can provoke central nervous system disturbances.

Due to lots of complications associated with these modalities of treatment such as systemic toxicity occured with medication, tube occlusion with transdermal coronary treatment and nonsurgical prospect patients for coronary artery bypass grafting etc. The applications of nanomedicine in the field of heart disease have been developed, Nanomedicine has potential strategy in dealing with these obstacles.

2. Nanomedicine

Recent progress in nanotechnology and their increasing needs day by day in biomedical field have developed the multifunctional nanoparticles. These nanoparticles, have the potential strategy to incorporate various functionalities, simultaneously these nanotechnology will provide; contrast for different imaging modalities, targeted delivery of drug or gene, and also thermal therapies. Although in the field of multifunctional nanoparticles has shown great importance in the emerging medical fields als.[15]

Nanoparticles are defined as those particles with diameter from 1 to 100 nm. The ideal size for nano drug delivery system is ranges from 10 to 100 nm.[16] Nanomedicine is nothing but it is a applications of nanotechnoly in medicine. In present days, nanotechnology has played an important role by delivering drugs to specific cells using nanoparticles. Targeted drug delivery is very essential to reduce the side effects of drugs with concomitant decreases in consumption and treatment expenses. The delivery of drug is mainly on maximation bioavailability for both at specific targeted directs in the body and at a specefic period of time. This can potentially be obtained by molecular targeting, and this can only be possible by using nanotechnology. Nanomedicine have developed the complex drug delivery mechanisms including the ability to get drugs through cell membranes and into cell cytoplasm.[17] Nanomedicine systems for coronary artery problem may be able to prevent tissue damage through influenced drug release; decreased drug clearance rates; or reduced the volume of dispersion and reduce the effect on non-target tissue.

2.1 How nanomedicine work against atherosclerosis

Nanomedicine, are generally molecular fabrications of organic or inorganic nanoparticles, are emerging as attractive nominees for therapeutic applications, Nanocarriers are desirable for cellular level medical care, because of nano size which is enough to interact with receptor targets with high particularity and eagernees, but are large enough to transport small molecule drugs and protect them from metabolic defusing, avoid renal clearance, and provide high surface areas that can be adorned with targeting ligands. these nanomedicine can be also allow chasing their distribution and thus it serve as diagnostic agents. Nanotechnology and the conception of synthetical nanomedicine have the chance to approach atherosclerosis therapies through 1) enhancing systemic circulation time of the carrier, 2) lowering drug toxicity, 3) enhancing drug solubility, 4) reducting the demanded dosage, 5) aggregating of imaging and therapeutic agents for review of disease progress, and 6) enhancing particular tissue aggregation through active or passive targeting.[18]

3. Development of nanomedicine and their function in coronary artery disease

Exploitation of nanoparticulate substances or nanomedicine in cardiovascular disease specially in coronary disease has gained increasingly wider acceptance because of local or directed delivery, prolonged effect of the drug, helped delivery into the erythrocyte, decrease of the shear effects of the blood flow.Therefore, it may be anticipated that nanomedicine will continue to contribute to developed diagnosis and treatment of atherosclerosis and other realated problems associated due to coronary disease.[19]

One of the main reason for application of nanomedicne in the field of coronary artery disease has been the directed due to visualization and therapy of atherosclerosis, The applications of nanomedicine in coronary artery disease has gained wider acceptance because of mainly specific drug or gene target molecular imaging. Polytherapy and imaging approaches are very useful in evaluating the delivery as well as therapeutic efficacy.[20]

In Recent development in nanodevices for nanomedicine have been widely achieved either by combination of older management methods with newer nanotechnology, or by implementing entirely novel techniques that have shown significant promise in the field. For example,More recently, the researchers Hyafil et al. have been shown the opening to envision macrophages in atherosclerotic plaques with CT imaging using N1177, a nanoparticulate formulation of iodine.[21] In 2006 Winter et al. from the Washington University School of Medicine (St Louis) has also been reported that inhibition of plaque angiogenesis by using paramagnetic perfluorocarbon nanoparticles.[22] A variety of molecular and cellular imaging techniques have been developed in the field of atherosclerotic plaque imaging and it may help to diagnosis of the disease, such as ultrasound, MRI, positron emission tomography, computed tomography,and single photon emission computed tomography.[23] Some of the materials which are used to enhance the visualization of inflammation and atherosclerotic plaques such as, liposomes polyamidoamine and diaminobutane, dendrimers and, gold nanoparticles quantum dots iron microparticles or dextran coated ultra small particles of iron oxide etc.[24]

3.1 Nanotechnology-channelize pointing of atherosclerosis

The majority of anticipating application of nanomedicine in vascular bundle is the targeting of imaging or therapeutic agents to atherosclerotic plaques. Advancement in atherosclerotic plaque have identified molecular visibilites of early-stage and late-stage plaques, and in colligation with available techniques to target nanopaticle carriers to specific plaque biometrics, presently investigated some of important molecular targeting site by nanoscale agents are listed in below;

3.1.1 Endothelial cells

Endothelial energizing with secretion of inflammatory particles, such as cell adhesion molecules (CAMs) and selectins, to advance the percolation of leukocytes between the membrane. This central expulsion on plaque walls cracks an opportunity as targeting by diagnostic and therapeutic agents at a identical former stage in plaque development. Selectins such as E- and P- selectin, enter in the beginning leukocyte-endothelial interactions in atherosclerosis, and their aim to hinder with antibodies can be employed to slow wound development. Nanoparticles with selectin ligands, such that the build effectively mime dispersing leukocytes, adhering to inflamed endothelium Such arrangement alter not only cures suppression of inflammatory bionic tracing the plaque, but also site-addressed release of therapies and imaging agents.[25]

3.1.2 Macrophages

The scavenger cell or macrophage has possible for both tending to repair and blasting effects within the plaque, and is thus a significant imaging and therapeutic target for nanoscale reagents, A predicting issuing nanotechnology for targeting the macrophage is mainly based on high-density lipoprotein (HDL). HDL effectively employed with arterial macrophages and can be organized to acquit nanoparticle line agents such as Quantum dot technology, (optical), gold nanoparticles (Computerized tomography), or iron oxide nanoparticles (MRI).[26]

3.1.3 Lipid Substance and Apoprotein

Extracellular lipid content and apoptosis of occupier cells induced by surplus cholesterol hyperemia and local ignition. These consequence will allow plentiful opportunities for stage-special directing of atherosclerosis. Along organizing the lipophilicity of counterpoint agents, mended targeting of lipid-ample plaque regions can be attained as MRI signal enhancement. Apoptosis can be supervised between the plaque by targeting disclosed phosphatidyl serine residues on apoptotic cell membrane folders applying the targeting protein annexin V. Targeting of annexin V, nanoparticles to apoptotic cells was certified to assist imaging of wounds employing CT and MRI, and annexin V targeting capacities can be readily consulted onto other nanoparticulate contrast agents, such as QD.[27]

3.1.4 Angiogenesis

A extensive scope of nanoparticles can be affluent with antiangiogenic drugs and conjugation with pointing ligands for plaque-particular suppression of blood vessel development. A especially-concerning approach for this determination is grounded on liquid perfluorocarbon nanoparticles accepting the angiostatic reagent fumaria. The fomite is conjugate with a novel $\alpha_v\beta_3$ integrin-targeted peptidomimetic agent to target adventitial neotoma and can also assume paramagnetic or optical contrast agents to alter chasing of the therapeutic. The nanoparticles displayed a sustained antiangiogenic force for up to 4 weeks when combined with co-occurrent statin therapy.[28]

3.2 Nanomedicine for the treatment or diagnosis of atherosclerosis

The management of coronary artery disease by applying small molecule pharmaceutics and common drug delivery methods is very objectional due to several biological barriers. specific Site- targeted delivery through the coupling of ligands, generally provides routes to ignore problems associated with conventional management access.Incorporation of complementary substances to the nanocephalic system can guide and centralize the therapeutic agent ,within diseased arteries. Some of recent formulated pointed nanomedicine for the treatment or diagnosis of coronary artery disease are described below,

3.2.1Crosslinked iron oxide nanoparticle

PEG (Poly-ethylene glycol) coated cross-linked iron oxide nanoparticles are developed for therapeutic or diagnostic of atherosclerosis it mainly target on Vascular Cell Adhesion Molecule-1(VCAM-1) cyclic peptide CVHSPNKKC via MRI image contrast.[29]

3.2.2. PEGylated lipids micelle

PEGylated phospholipid is a novel fibrin-targeted paramagnetic molecular imaging system that, has the ability to enhance the catching of intravasation clots and instant thrombi between arteries which may lead to cause of active dangerous plaques, because of its strong MR contrast impact.[30]

3.2.3.Dextran-coated iron oxide nanoparticles

The dextran coating iron oxide nanoparticle promotes their impute by macrophages by scavenger receptor-mediated endocytosis. Also, the phagocyte scavenger receptor-mediated endocytosis can be directly targeted by using monoclonal antibodies, providing significant enhancement of wound signal chroma in T1-weighted MRI.[31]

3.2.4.Paramegnatic nanoparticle

Paramagnetic nanoparticles incorporating an angiostatic drug against integrin cell division, which are most significant in upregulation of angiogenic endothelium during tumor growth. This nanoparticle targeted directly on peptidomimetic $\alpha_v\beta_3$ integrin via MRI signal enhancement.[32]

3.2.5. PEGylated-DSPE

PEGylated-1,2-distearoyl-sn-glycero-3-phosphoethanolamine(phospholipids)inconjunction with other lipid-targeting ligand like tyrosin, it construct multimodal micelles for targeting lipid-rich areas of plaques for imaging and treating atherosclerosis by the way of MRI signal enhancement.[33]

3.2.6 .PLA-paclitaxel conjugate nanoparticle

Combination of PLA-paclitaxel conjugate inside a lipid-PEGylated lipid may also help in inhibition of vascular smooth muscle proliferation by targeting Collagen-IV targeting peptide KLWVLPK, following percutaneous angioplasty.[34]

3.2.7. Monocrytalline iron oxide nanoparticle

The development of monocrystalline iron oxide nanoatoms assist to acquit iron oxide MRI external the boundaries of passive targeting by tissue aggregation and particle phagocytosis to ligand-conducted or active transport.Inside a dextran shell internalization of monocrytalline iron oxide nanoparticle may immediately targeted on dextran receptor SIGNR1.[35]

3.3 Nanomedicine-grounded operative devices

Nanomedicine has also been enforced for improving the achiver of surgical procedures applicable to the treatment of atherosclerosis. To bettered the drug delivery ambit of drug-washing tubes, polymer needles can be joined on the stent surface to help thicker penetration of therapeutics for contracted lesion reveal. As an auxiliary to stent angioplasty, along comprising a magnetically sore admixture into blade intravascular stents, endothelial cells affluent with paramagnetic nanoparticles were conducted toward the stent surface below a local magnetic field, thus enhancing re-endospore.[36]

4. Problems with Nanomedicine in treating CAD and Future strategies

The uncomparable advantages of nanomedicine also have some restrictions mainly because nanoparticles evedience clear-cut differences linked to larger particles referable to their nano size.The possible toxicity of the nanomedicine can be difficult to evaluate because it involves exhaustive checkup of each material singly and their combinations also.Nanomedicine toxicity can be impacted by lots of factors, like as materialconstituation, shape, size, bearing of functional groups, surface charge and solubility etc.[37] In summation, their larger surface-to-volume ratio effects in enhanced chemical and biological action which may conduct to the produced of Reactive oxygen species (ROS) and cause serious damage of DNA, RNA and proteins.[38] A suitable assign when planning nanomedicine for targeted delivery is the increased spreading time, which alter the DDS to successfully deliver the therapeutic agent to the objective area. Even so, lengthy circulation time increases the possibility of contact between nanodrug and coagulating factors and this interactions may cause to platelet aggregation and formation of thrombus in blood vessels.[39] Platelet activation was mainly depending on the size of dug.Platelet activation is intermeadiated mainly by platelet glycoprotein integrin $\alpha_{IIb}\beta_{3.}$ Generally micro-sized atoms acatuate protein kinase C (PKC), although nano-sized similitudes, in a PKC dependent mode. In addition, it was foregrounded that carbon based nanomedicine accelerated platelet activation in the absent of thromboxane A2 and adenosine diphosphate release.[39] This is certified that nanomedicine may act with factors of the coagulation scheme through totally different indicating pathways and it may change gene aspect, which may prove a dispute for evaluating their biocompatibility**.**

Polymer and polymer-lipid based nanomedicine are rising as prediciting new prospects for the direction of atherosclerosis. Well-informed design and composition tractability in colligation with developed targeting and pharmacokinetic attributes are some of the prominent attributes of polymer based nanomedicine. Atherosclerosis is a central disease, it is particularly important to have targeted therapy in order to behind and consume possibly of turned the disease development. With the improvement of controlled release drugs and nanomedicine that can preclude vascular reconstructing conducting to blood vessel occlusion, new choices could be visualized that replace drug-rinsing stents. However various disputes will need to be defeat, admitting the barriers for i.v administration and effective targeting that can put off, previous authority**.** Similarly, drug carrying particles are frequently designed with the aim to deliver after an ischemic effect or cardiovascular treatment. These target development of new blood vessel in growing wound or restenosis following by suppressing cell ontogenesis.

DISCUSSION AND CONCLUSION

The simultaneous development of the cognition base of atherosclerosis and the design of nanomedicine allows for the conception of factors specifically intentional to enhance the diagnosis and treatment of coronary artery disease. Major areas of center have admit molecular targeting, stent engineering, therapeutic neotoma, biosphere for detecting of disease-particular biomarkers, and the tackling of plaque homing cells for imaging and therapy. A succeeding destination is the development nanmedicine able of allowing for clinical resubmit by interact with multiple stage-specific medicine, or the involving and temporal release of therapies in reaction to molecular prompts. Designing nanomedicine drug or polymer based systems to disrupt the indicating cascade at multiple clients would be an efficient way to inhibit disease progress. Specific targeting to growing wound could be deflect by some of the increased susceptibility to infection checked with anti-cytokine treatment.

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