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PERSPECTIVE

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Therapeutic potential role of vitamin C in prevention and control of heart transplant rejection and cardiac allograft vasculopathy. A need for consideration

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Abstract

The burden of cardiovascular diseases is rising rapidly globally. Heart transplant is one of the most last resort medical option for patients with heart failure. Unfortunately, this surgical intervention is associated with several serious complications including heart transplant rejection (HTR) and Cardiac Allograft Vasculopathy (CAV) which can manifest just within few years' posttransplant. These complications affect significantly the prognosis and quality of life among postheart transplant patients. Several medications including immunosuppressant, antibiotics, antihypertensive, and statins have been used during posttransplant care so as to address such complications. Unfortunately, most of those drugs are expensive and pose a number of serious side effects to the patients enough to compromise patients' quality of life too. Several studies on Vitamin C are therapeutically suggestive that it can be used during postheart transplant care with more cost-effective benefits with less and minimized side effects compared to the current drugs in place. It should be considered pharmacologically that Vitamin C has a great potential role clinically in prevention and control of HTR and CAV development. On the light of such findings as described above, we recommend more studies especially clinical trials and molecular studies to determine whether Vitamin C can be repositioned to replace or to be used along the current drug regimens used in postheart transplant care for prevention and control of HTR and CAV.

KEYWORDS

cardiac allograft vasculopathy, cardiovascular diseases, heart transplant, heart transplant rejection, vitamin C

1 | INTRODUCTION

Cardiovascular diseases (CVDs) refer to disorders that affect the heart and blood vessels. They include coronary artery disease, stroke, heart failure, and peripheral artery disease.[1] With an estimated 17.9 million deaths per year, they are among the greatest cause of deaths worldwide in 2019 which accounted for 32% of all global deaths and 38% of all premature deaths secondary to noncommunicable diseases.[1] Deaths from heart diseases in particular have remained the top cause of mortality worldwide for the past 20 years.[2]

The goal of preventive measures is to reduce modifiable risk factors. Approaches may include quitting smoking, eating a nutritious diet, getting regular exercise, and managing chronic conditions like hypertension, diabetes, and hyperlipidemia.[1] Medication, lifestyle modifications, and in certain cases surgical treatments may be used to treat CVDs.[3] In some cases, patients with CVDs may end up with heart failure.

Among available definitive treatment modalities for heart failure, heart transplantation is the gold standard.[4,5] A heart transplant is a surgical procedure that removes a sick heart and replaces it with a healthy heart from a deceased donor to prolong life and improve quality of life.[6] This surgery is carried out in individuals with end-stage heart failure who continue to experience symptoms despite receiving proper medical treatment.[6] With a median longevity of 12.2 years, the 1-year survival rate following cardiac transplantation is now above 90%.[7]

However, heart transplant procedure is associated with a number of complications ranging from intraoperative up to 5–10 years after transplant.[6] Acute rejection, malignancy, infection, Cardiac Allograft Vasculopathy (CAV), and renal insufficiency are just a few of the conditions that might significantly affect how a heart transplant will turn out.[8]

CAV is one of major complications and cause of morbidity and mortality in heart transplant recipients.[9] It is one of the top three causes of death during the first year following transplantation and it is seen as a chronic fibroproliferative rejection against the transplanted heart mediated through immunologic, inflammatory, and nonimmunologic mechanism which compromise cardiac functioning by narrowing of coronary vessels.[10,11]

Key Points

- Heart transplant procedure is associated with a number of complications ranging from intraoperative up to 5–10 years after transplant including acute rejection, malignancy, infection, Cardiac allograft vasculopathy (CAV), and renal insufficiency which cause increased morbidity and mortality in heart transplant recipients.
- Immunosuppressive drugs, statins, antihypertensives and antibiotics are used in maintaining the implanted heart to reduce the risk of heart transplant rejection (HTR) and CAV development.
- Unfortunately, most of these drugs are expensive and have been associated with a number of serious side effects enough to compromise patients' quality of life.
- Several studies on Vitamin C are therapeutically suggestive that it can potentially be used during postheart transplant care in prevention and control of both HTR and CAV with more cost-effective benefits therapeutically with minimized side effects.

2 | HEART TRANSPLANT REJECTION (HTR)

HTR happens when the recipient's immune system mounts an immunological reaction to the foreign antigens in the donor organ specifically the heart in this case.[6] HTR continues to be the biggest drawback of heart transplantation despite advancements and better overall results.[6] HTR may result from either early graft dysfunction, which happens within the first 24 h, or late graft dysfunction, which appears weeks to years following transplantation, depending on timings.[6]

HTR can take three different forms: hyperacute rejection, which occurs intraoperatively right away as the aortic cross-clamp is released and the donor heart is exposed to the recipient's red blood cells, followed by acute cellular rejection which is T cell-mediated reaction and most commonly 12 months after the surgery, and finally antibody-mediated rejection.[12] However, hyperacute rejection is becoming less common as a result of blood type and panel reactive antibody cross-matching.[12] Controlling allograft rejection, minimizing immunosuppressant side effects, adjusting to the transplantation process, and reintegrating the patient into society are the four goals of posttransplantation treatment.[13]

Following transplantation, immunosuppression is usually achieved with a triple therapy regimen consisting of corticosteroids, purine synthesis inhibitors, and calcineurin inhibitors.[12,14] The majority of patients are maintained on steroid therapy for life after heart transplant.[15] Steroids modify the expression of genes involved in the immunological and inflammatory response through transcriptional regulation.[16] Corticosteroids are usually prescribed in high doses.[12] Among adult heart transplant recipients who survive the first-week postheart transplant, increase in prednisone dose is associated with increased mortality.[17] Long-term use of immunosuppressant drugs including steroids are associated with both cosmetic, metabolic adverse effects and increased risk of malignancy development.[16,18] Cosmetic effects include hirsutism, acne, easy bruising, skin fragility, moon face, buffalo hump, weight gain, and truncal obesity. Important metabolic effects are hyperlipidemia, salt and water retention, diabetes mellitus, osteopenia, and growth retardation in children. Long-term administration of steroids may result also in chronic adrenal suppression, and adrenal insufficiency can follow a steroid taper or “stress” (illness, surgical procedures, infections).[16]

Management of HTR faces a number of challenges. Early detection of graft rejection is the primary challenge because patients are sometimes asymptomatic and rarely, they can present with nonspecific extra-cardiac symptoms such as fever.[19] Moreover, the use of prolonged use of immunosuppressant drugs increase the chances of developing opportunistic infections among this population of patients.[16]

3 | CAV

CAV is the main complication in late graft loss and is an immune-mediated pathologic remodeling of the vasculature in transplanted hearts.[20] CAV and late graft failure accounts for the majority of

patient mortality at 5–10 years, more than malignancy does.[21] At the time of allograft implantation, its incidence rises over time, reaching 29.3% at 5 years and 47.4% at 10 years.[22] Graft malfunction happening more than a year after transplantation should always be evaluated for CAV.[23]

The two groups of risk factors for CAV development are immune and nonimmune. The organ donor's old age, sex, explosive brain death, cytomegalovirus (CMV) infection, ischemia/reperfusion injury, hypertension, diabetes mellitus, hypercholesterolemia, and obesity are nonimmune risk factors for CAV.[20,24] The immunosuppressive medications' side effects, which includes the development of posttransplant diabetes mellitus, hypertension, hyperlipidemia, nephrotoxicity, and a rise in CMV infections are the known nonimmune risk factors for vasculopathy. These can indirectly lead to CAV.[25]

The management of CAV currently remains limited and incomplete, and is mostly focused on preventative measures, and taking statins and mTOR inhibitors to slow the progression of the illness.[20,21] Mycophenolic acid and mTOR inhibitors (sirolimus and everolimus) reduce the development and progression of CAV.[20]

Reduced cold ischemia duration and subsequent tissue damage, enhanced myocardial preservation during storage and transit of the graft, and prevention of endothelial harm during brain death before transplantation all contribute to improved posttransplant cardiac performance and longevity. Literatures show that the use of antihypertensive medicine slows the advancement of CAV, even if there isn't much proof that posttransplant hypertension causes it.[20]

In light of their capacity to delay immunologic processes associated with CAV, immunosuppressive medications have been considered for medical therapy of the disease.[24] So to modulate immune-risk factors, patients are started on calcineurin immunosuppressive medications, most commonly cyclosporine, right after transplantation.[26] Unfortunately, taking cyclosporine at high doses and for a long period of time might have some side effects that include hypertension and renal failure.[26] Leflunomide, rapamycin, and mycophenolate mofetil are examples of immunosuppressive medications that can be used as alternative to cyclosporine to prevent CAV by restricting the proliferation of smooth muscle cells.[26] Hyperlipidemia is known to be a risk factor for both CAD and CAV.[26] Sadly, hyperlipidemia can result from using corticosteroids, cyclosporine, rapamycin, and to a lesser extent tacrolimus and everolimus.[23] On addition to preheart transplant risk factors for hyperlipidemia, this necessitate the need of lipid-lowering medications since lifestyle changes at this stage typically are not adequate enough to bring lipid profiles down to the required values.[26]

The most widely used form of HMG-CoA reductase inhibitors, known as statins, is very successful at reducing total cholesterol, low-density lipoprotein (LDL) and very low-density lipoprotein while raising high-density lipoprotein.[26] Statins may prevent fatal rejection episodes, decrease terminal cancer risk, and reduce the incidence of coronary vasculopathy.[27] The use of statins beginning 1–2 weeks after heart transplant is recommended regardless of cholesterol levels and statins should be used as part of standard therapy in patients after heart transplantation.[28,29] Myalgia is the most common side effect and rhabdomyolysis is the most serious adverse effect from statin use and is very rare and some statin drugs are potentially diabetogenic and the risk appears to increase in those on higher doses.[30]

And then, during each posttransplant patient visit, the management of hypertension, glycemic control, quitting smoking, exercise training, and CMV prophylaxis are reiterated because these are classic atherosclerotic risk factors that contribute to CAV advancement.[20,21] Retransplantation is only the choice for patients with diffuse, multivessel coronary artery disease who have severe graft dysfunction, clear signs of heart failure, or ischemia, and who do not have any retransplantation-related contraindication.[23]

4 | HTR, CAV, AND ASCORBIC ACID (ASC)

A vital nutrient known as ASC functions as both an antioxidant and a cofactor in several biological enzymatic processes.[31] It bears pleiotropic activities associated with its capacity to transfer electrons but unlike the majority of mammals, humans are unable to synthesize it.[31,32]

Vitamin C supports different cellular processes of the innate and adaptive immune systems, which aids in immune protection.[32] Vitamin C helps the skin's oxidant scavenging capacity and epithelial barrier function against infections, potentially defending against oxidative stress from the environment.[32] An accumulation of vitamin C in phagocytic cells, including neutrophils, can promote chemotaxis, phagocytosis, the production of reactive oxygen species (ROS), and eventually the death of microorganisms.[32] Vitamin C shows antimicrobial effect both in vivo and in vitro, which is dose-dependent and is associated with induction of ROS production,[33,34] Furthermore, vitamin C exhibit both immunomodulatory and antimicrobial property effectively against viral, parasitic, fungal, and viral infections even with multidrug-resistant strains.[35]

A deficiency in vitamin C lowers immunity and increases susceptibility to infections.[32] As a result of increased inflammation and metabolic demands, infections have a considerable negative influence on vitamin C levels. Additionally, vitamin C supplements seem to be helpful to both prevent and treat systemic and respiratory infections.[32] It can restore normal antiviral immune system and can suppress significantly the inflammatory cytokine storm.[36–38] It auto modulate production of cytokines and monocyte and lymphocyte proliferation, which means when they are high, it boosts the level up and when they are so high, it brings them down.[39] It is suggested that high dosages of vitamin C keep plasma corticosteroid levels high, which could lower an organism's immunological response when stress is present.[40]

A meta-analysis of 13 clinical trials found Vitamin C supplementation lowered significantly the LDL cholesterol and triglyceride concentration.[41] A minimum of 4 weeks supplementation with 500 mg/d of vitamin C can result in a considerable reduction in the levels of triglycerides and LDL cholesterol in the blood.[41,42] Through improving endothelial functioning in patients of high risk like in

Diabetes, Vitamin C reduces risk of developing cardiovascular complications.[42]

A meta-analysis of RCT showed that Vitamin C supplementation kept both Systolic Blood Pressure and Diastolic Blood Pressure (DBP) in control.[43] Another systematic review and meta-analysis found Vitamin C supplementation resulted in a significant reduction of blood pressure in patients with essential hypertension.[44] Moreover, Vitamin C can act as anticoagulant agent (blood thinners), but care should be taken since Vitamin C can interact with Warfarin and cause coagulopathy too.[45,46] It was also shown that Vitamin C supplementation significantly lowered Serum uric acid.[47]

Adhesions formation in the heart occurs as result of HTR through inflammation process.[6] These adhesions can be a serious cause of CVA development.[20,48] Vitamin C has been shown to reduce postoperative adhesions formation significantly in rats' models.[49,50] This makes Vitamin C one among the antiadhesive agents. Moreover, Vitamin C has been found to exhibit chemotherapy properties against cancer and improved cancer patients' condition.[51–53]

Vitamin C supplementation is contraindicated in blood disorders like thalassemia, G6PD deficiency, sickle cell disease, and hemochromatosis.[54] Epidemiologic data have shown a correlation between vitamin C intake (dietary and supplemental) and oxalate kidney stones in males, especially at very high doses. Therefore, routine supplementation is not recommended in men or, more specifically, in any patients who are at risk of developing oxalate stones.[55]

5 | DISCUSSION

Cardiac transplant is the lifesaving procedure in patients with end-stage heart failure. The postoperative phase, however, can be difficult because of potential issues like rejection, infection, ischemia-reperfusion injury and CAV.[6] Immunosuppressive drugs, statins, antihypertensive drugs, and antibiotics are used in maintaining the implanted heart to reduce the risk of HTR and CAV development.[12,14] These drugs have been used for a long time and they have been helping patients to accommodate these implanted hearts.[14] Unfortunately, most of these drugs are expensive and have been associated with a number of serious side effects as discussed above which can compromise the quality of patients' lives.[16,18]

These drawbacks can be therapeutically replaced alternatively or along the standard management with the cost-effective approach to a great extent by the use of Vitamin C postheart transplant as discussed above. Vitamin C has quite a number of benefits and less side effects compared to the current drugs utilized in management/care of postheart transplant apart from being readily available (cheap) and its therapeutic abilities to replace most of the drugs used. Vitamin C has an broad antimicrobial effect even against multidrug-resistant strains, being used as a prophylaxis will enhance effectiveness in infection prevention after transplantation.[32,35,56]

Vitamin C has immunomodulatory ability and can suppress inflammatory cytokine storm significantly.[35–39] This makes Vitamin C a strong therapeutic candidate as immunosuppressive drugs to be used postheart transplant. Vitamin C also lowers bad cholesterol and triglycerides significantly, it can act as anticoagulant agent (blood thinners), it keeps both systolic and DBP in control, lowers risks of developing cardiovascular complications, it lowers serum uric acid and has anti-inflammatory effect as well.[41,42,45–47,57] All of these features make it a good replacement for majority of drugs used postheart transplant care. Moreover, antiadhesion formation property and chemotherapy ability of Vitamin C adds credits to its therapeutic value as a prophylaxis against adhesion formation and malignant development postheart transplant.[49–53]

6 | CONCLUSION AND RECOMMENDATION

Heart transplant is associated with several serious complications including HTR and CAV which can manifest just within few years' posttransplant. These complications affect significantly the prognosis and quality of life among postheart transplant patients. Several medications including immunosuppressant, antibiotics, antihypertensive, and statins have been used during posttransplant care so as to address such complications. Unfortunately, most of those drugs are expensive and pose a number of serious side effects to the patients enough to affect their quality of life too.

Several studies on Vitamin C are therapeutically suggestive that it can be used during postheart transplant care with more cost-effective benefits and with less side effects compared to the current drugs in place. It should be considered pharmacologically that Vitamin C has a great potential role clinically in prevention and control of HTR and CAV development. On the light of such findings as described above, we recommend more studies especially clinical trials and molecular studies to determine whether Vitamin C can be repositioned to replace or to be used along the current drug regimens used in postheart transplant care for prevention and control of HTR and CAV.

AUTHOR CONTRIBUTIONS

Idd J. Kenedy: Data curation; writing—original draft. **Jaynes F. Kabuhaya**: Data curation; writing—original draft. **Harold L. Mashauri**: Conceptualization; data curation; methodology; project administration; supervision; writing—review and editing.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

TRANSPARENCY STATEMENT

The lead author Harold L. Mashauri affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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