

Human Umbilical Cord (HUC) Vessels: A Novel Substitute for Arterial Bypass Grafting

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ABSTRACT

Human Umbilical Cord (HUC) vessels and Wharton's jelly containing Mesenchymal Stem Cells may novel substitute for coronary vessels in reconstructive Coronary Artery Bypass Grafting (CABG) surgery. In developing countries, ischemic cardiac tissue injury-related mortality is higher than in developed countries. Organ and tissue transplants may amend the disease but the availability of donor tissue, tissue matching, and procurement of organs are important parameters for successful grafting. Allogenic or autologous preserved HUC vessels along with Wharton's jelly containing MSCs having human Cord Lining Epithelial Cells (CLECs) which did not express the MHC class II antigen HLA-DR but the non-classical MHC class I antigen HLA-G and HLA-E lacked. HUC-MSc also expresses exosome, Smad protein, TGF beta, BMP also helps in cardiomyocytes regeneration and neo-vascularisation. So the chances of graft rejection is lower and long term survival of graft also initiated. Therefore, human umbilical cord may be used as a substitute for artery or venous graft of vascular and reconstructing surgery. Moreover, chances of recurrent surgical or interventional is diminished for maintaining the patency of coronary vessels.

Keywords: Fetal stem cell; Immune tolerance; Coronary artery bypass grafting; Transfusion transmitted infection

Abbreviations: HUC: Human Umbilical Cord; MSC: Mesenchymal Stem Cells; HLA: Human Leukocyte Antigen; HUV: Human Umbilical Vein; PCI: Percutaneous Coronary Intervention; CABG: Coronary Artery Bypass grafting; TTI: Transfusion Transmitted Infection; CAD: Coronary Artery Disease

INTRODUCTION

Coronary Artery Disease (CAD) is a most common cause of death and disability in developed and developing countries. Globally 17.5 million deaths have been noted in 2012 [1] due to this disease. More than 75% of deaths, observed in developing countries. Mortality related to cardiovascular disease is decreasing rapidly in developed countries. Whereas death or disability related to myocardial disease as been increasing in developing countries due to industrialization, urbanization, food habit changes and changes in the lifestyle of people [2,3]. Percutaneous Coronary Intervention (PCI) or Coronary Artery

Bypass Grafting (CABG) is the gold standard treatment for ischemic heart disease patients. Organ and tissue transplants may amend the disease but availability of donor tissue, tissue matching and procurement of organ are important parameters for successful graft.

Recently Human Umbilical Cord (HUC) has been broadly studied and current studies have revealed that HUC may be the potential substitute of vessels [4-7], ligaments [8], tendon and bone [9,10]. Human Cord Lining Epithelial Cells (CLECs) does not express the MHC class II antigen HLA-DR whereas the non-classical MHC class Ib antigen HLA-G and HLA-E has a few immunomodulatory roles. HLA-G protein decreases CD8 and

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natural killer cells production. Therefore, human umbilical cord may be used as a substitute for artery or venous graft of vascular and reconstructing surgery.

HYPOTHESIS

We hypothesise that the vessels of Human Umbilical Cord (HUC) may be an effective novel substitute for reconstruction of the coronary artery for those having coronary artery diseases as well as peripheral vascular disease. Our hypothesis can be summarised as follows:

1. Allogenic substitute: Human umbilical cord, as a natural tissue product for reconstruction of the diseased coronary artery. It is collected from Transmission Transmitted Disease (TTD) screened mother of neonate right after parturition in a sterile manner. Umbilical arteries/veins help in surgical reconstruction of damage vessels to another person. HUC containing two arteries and one vein. It is also established that the HUC is a good source for Mesenchymal Stem Cells (HUC-MSCs) which can be differentiated into multiple lineage-specific cells that form bone, cartilage, liver, cardiac tissue etc [10,11]. Moreover, it is also established that the Wharton's jelly that surrounds the Human Umbilical Vein (HUV) is rich in growth factors [12]. Thus HUC, with such a composition of MSC, living cells and growth factors, might be a promising material for restoration of the function of coronary artery

2. Autologous substitute: An individual's umbilical cord of patients, banked right after birth can come in handy for future use. It could be directly applied to directly reconstruct the patient's own coronary artery. We hypothesise that the autologous HUC may also be used to reconstruct the coronary artery. The autologous HUC offers the following advantages: Firstly, the HUC-MSCs might differentiate into myocardial cells *in vivo* after transplantation, which might promote the collaterals regeneration. Secondly, replacement of the scared myocardial tissues by helping regeneration of new viable cardiac tissue without any immunologic graft rejection can also be predicted.

Both allogenic and autologous substitute can be used to reconstruct the coronary artery without altering the normal cardio vascular anatomy. This operation does preserve the myocardial contractile function. Furthermore, the HUC is long enough to reconstruct the coronary artery more than once, if necessary (e.g., in case of postoperative anastomotic stricture).

EVALUATION OF THE HYPOTHESIS

The feasibility of this hypothesis is based on the following four facts:

1. Scaffolds: The diameters of umbilical vessel 3 mm to 4 mm and coronary vessels 3.20 mm to 4.08 mm in diameter [13] are similar. Mature HUC attains an average diameter of 1.7 cm and

a length of 50 cm-60 cm. The diameter of umbilical artery varies from 3 mm and 4 mm, and the diameter of umbilical vein ranges between 6 mm to 8 mm. The normal coronary artery has a diameter of 6 mm or less, with a range of 4 mm-8 mm in adults. After choosing the umbilical vessels with the appropriate diameter, cells and Major Histocompatibility Complex (MHC) antigens can be removed to reduce immunogenicity without performing the process of decellularisation because chemical treatment of HUC-MSC may lose the valuable cells and Extracellular matrix [14].

2. Seed cells: The HUC, especially the part of Wharton's jelly and HUC vein, is an abundant resource of Mesenchymal Stem Cells (HUC-MSCs) [15,16]. It is generally accepted that HUC-MSCs are poorly immunogenic with multilineage differentiation potential [15,16]. Recently, HUC-MSCs have successfully differentiated into osteocytes [17], cardiomyocytes, etc. HUC-MSCs have capacity to self-renewal and regenerate cardiomyocytes and other essential epithelial cells of myocardium.

3. Growth factors: MSCs and Wharton jelly helps in liberation of various growth factors, those are responsible for proliferation and differentiation of cells. For example, Epidermal Growth Factor (EGF) exerts a wide variety of biological effects, including the promotion of proliferation and differentiation of MSCs [18,19]. Transforming Growth Factor Beta (TGF- β) plays important roles in cellular differentiation, BMP hormone secretion and immune function [18,19]. Fibroblast Growth Factor (FGF), EGF and TGF- β have been detected in the extracts of Wharton's jelly [20].

4. Sources: The HUC is abundant in resource without ethical issues. It is usually discarded after delivery. Screened collecting the HUC after birth in sterile way does not carry any risk to the mother or new born. Some of investigators have been suggested the importance of banking the whole umbilical cord unit for research or future use in therapeutic purpose [21].

5. Collection, preservation and cryopreservation: Human umbilical cords obtained from the OT and were immediately stored at 4°C post-delivery. The whole processing of the umbilical artery/vein should start within 24 hours of its collection. Using a sharp dissection needle, the umbilical cords are removed under sterile conditions [22,23]. The decellularized or *de novo* cord blood vessels for vascular or surgical reconstruction and tissue engineering scaffolds, the saline cryopreservation medium composed of DMEM/ α -MEM/EGM in presence of FBS and PenStrep can be used for storage at -20°C and the ratio of the volume of the cryopreservation medium and that of the umbilical vessel is maintained at 20:1 at a cooling rate of 1°C/min through vitrification and slow cooling process [24,25] (Figures 1 and 2).

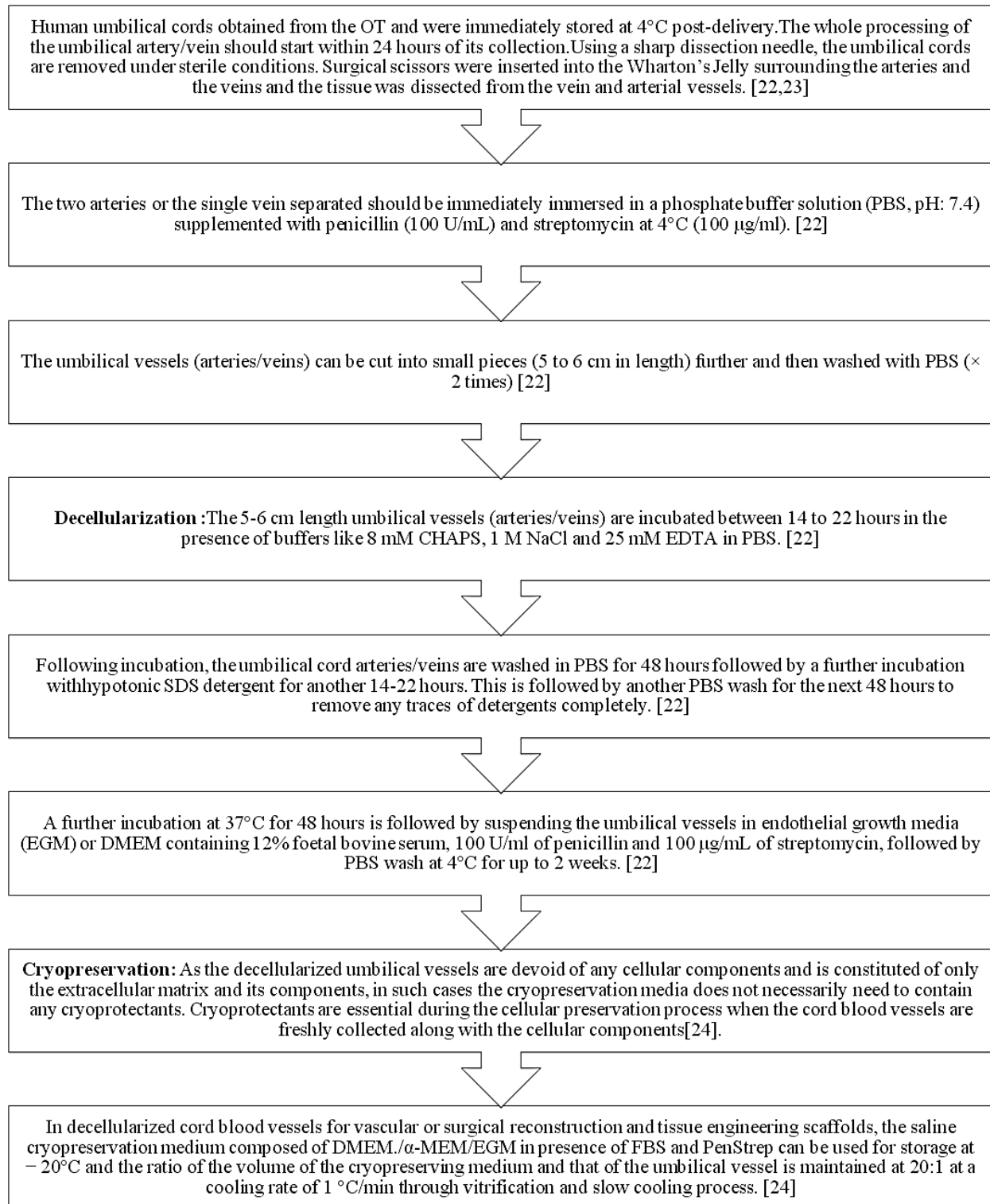


Figure 1: Collection and isolation of the cord blood vessels (arteries and veins).

The above protocol is for cryopreservation of umbilical cord blood derived vessels which includes both arteries and vein used as a biomaterial for vascular constructs and tissue engineering applications. This protocol does not include the storage of the freshly collected umbilical cord containing the cellular components of the vessels [24].

Investigations have shown that slow cooling process is favourable than vitrification process of freezing the umbilical cord vessel as

slow cooling helps in maintaining the intact architecture of the umbilical cord blood tissue and has shown cell proliferation *in vitro* when fresh samples along with the cellular components are cryopreserved [25]. Efficiency of the decellularized human umbilical artery can be assessed with time to time DNA histology and assay staining protocol before and after cryopreserving [22-24].



Figure 2: Collection of umbilical vessels from placenta.

DISCUSSION

Allogenic ABO matched with recipient or autologous preserved at -120°C Human Umbilical Cord (HUC) vessels are used for surgical reconstruction. Autologous or allogeneic Umbilical artery/vein is preferable considering the diameter of existing coronary vessels of recipients. Preserved autologous umbilical cord vessels used for reconstruction after thawing at normal room temperature. Sclerosed or atheromatous narrowed segmental coronary vessels reconstructed with patent umbilical vessels (Figure 3). HUC derived mesenchymal stem cells after surgical vascular reconstruction as an alternative to coronary vessels helps to maintain the vascularity of cardiomyocytes. Exosomes of HUC MSC helps in the release of Smad protein from the intracellular part of viable cardiomyocytes. Smad protein helps in signal transduction from extracellular to intracellular space with the help of Transforming Growth Factor Beta (TGF Beta). After signal transduction Smad protein helps in gene transcription. Transcription of genes improves the cardiac systolic function by protecting myocardial cells from apoptosis and by promoting angiogenesis by expression of Bcl-2 family [26,27]. Exosomes also promote cell repair through regulating Smad7 in cardiomyocytes [24]. HUC MSC derived TGF beta and BMP also in self renewal and maintenance of cardiac electrophysiology by various means [28,29], given in Figure 4.

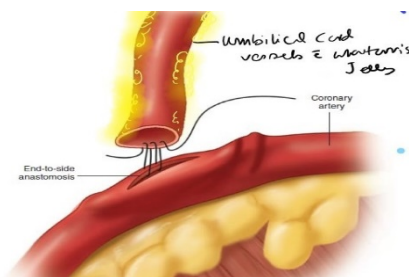


Figure 3: Umbilical vessels with Wharton’s jelly uses as reconstruction of Coronary artery.

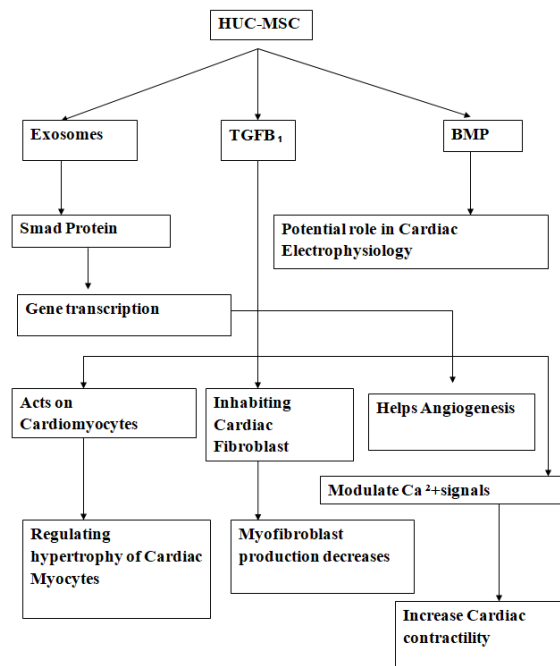


Figure 4: Mechanism of cardiomyocytes regeneration.

CONCLUSION

We hypothesise that the HUC may be a novel substitute for CABG or any other vascular surgery, which also reduces morbidity and DALI (Disability Associated Life Index).

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CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this paper.

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