Human Amniotic Membrane for Pericardium Substitute in Cardiac Surgery Patients

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Background and Significance

Post-operative atrial fibrillation (POAF) is a common and potentially serious complication following cardiac surgery. Between 20-50% of patients experience atrial fibrillation (AF) often during the first week after surgery.[1-4] POAF is not a benign condition. It is associated with a two- to four-fold increased risk of readmissions, renal failure, stroke, pacemaker implants, and bleeding.[5-7] In addition, POAF carries a two-fold increase in all-cause 30-day mortality.[5-10] POAF has long term implications. Of cardiac surgery patients who experience new onset AF, 18% had late AF at 1 year follow up, while 36% had AF at 5 years, and 55% had AF at 10 years.[11] Accordingly, POAF may be an indication of an underlying myocardial substrate and represent a risk factor for developing sustained AF, rather than an unrelated post-surgical complication. POAF is not limited in its impact during the perioperative period, but rather, is associated with 4-fold risk of stroke and a 3-fold increase in all-cause mortality at 1 year.[12,13] Patients who develop POAF incur on average $10,000-$20,000 in additional hospital treatment costs, 12-24 hours of prolonged ICU time, and an additional 2 to 5 days in the hospital.[14,15] Indeed, the socioeconomic impact is profound. Healthcare costs related to the care of patients with POAF in the US are estimated at over $1 billion annually.[4]

Several prospective epidemiological studies have linked local and systemic inflammation with an increased risk of AF. The serological markers that have been most frequently studied are high-sensitivity C-reactive protein (CRP) and interleukin (IL)-6.[16-18] Additional support for this concept has been suggested by multiple studies demonstrating decreased rates of POAF in patients who receive anti-inflammatory prophylaxis using corticosteroids.[19,20] A growing body of literature details the unique features of the local intrapericardial postoperative inflammatory milieu after cardiac surgery as a possible contributor to POAF.[21-23] Post-cardiotomy pericardial fluid has large (4 to 700-fold) increase of multiple circulating inflammatory factors, including tumor necrosis factor-α, neutrophil-gelatinase–associated lipocalin, myeloperoxidase, oncostatin M, and Metalloproteinases (MMP-9). [22] Postoperative pericardial fluid is highly oxidative and contains blood, hemolyzed blood cells, free hemoglobin, and high levels of inflammatory markers reflective of leukocyte and platelet activation.[23] Contact between inflammatory cells and cardiac tissue likely plays a role in the pathogenesis of POAF but the mechanisms of this interaction remain unknown. Animal models have illustrated that the incidence of POAF is directly correlated to the degree of inflammation of the atria and around the heart.[24] Use of active clearance chest tubes has been shown to decrease incidence of POAF.[25] Closing the pericardium following cardiac surgery also reduces the incidence of POAF.[26,27]

There are several reports of human amniotic membrane (AM) reducing inflammation,[28-30] having antimicrobial properties,[31,32] and low risk of immunogenicity.[33] This makes it an ideal biocompatible scaffold widely used for the treatment of several conditions, including intractable epithelial defects, burns, diabetic/ peripheral vascular ulcers, partial limbal cell deficiencies, peripheral nerve regeneration, tendon repair and Stevens-Johnson syndrome.[34-40] AM is being used at our institution as a clinical tissue allograft in burn patients, for digital ulcers in scleroderma patients,as a nerve wrap to protect nerves from adhesions post-surgery, trachea stenosis-tracheal stent covering.

Specific Aims

Cardiopulmonary bypass triggers a systemic and localized inflammatory response which has been shown to serve as a trigger for POAF onset. Some evidence further suggests that releasing the heart from its natural pericardial restraint can augment this response.

The Cell Therapy and Regenerative Medicine Program (CellReGen) at the University of Utah manufactures sterile AM for human use which is currently used to enhance wound healing, particularly in burn patients. Early investigation by our basic science laboratory has demonstrated that placement of AM on rat hearts after myocardial infarction can decrease myocardial scarring.

The primary objective of this research endeavor is to determine the safety of AM as a pericardial substitute in cardiac surgery with a secondary aim as to whether application of AM decrease the incidence of POAF following cardiac surgery. We hypothesize that application of AM at the time of cardiac surgery will decrease inflammation and the subsequent substrate for the development of POAF. In order to test this hypothesis, we

propose a pilot clinical trial in patients undergoing cardiac surgery at the University of Utah with the following specific aims:

Aim 1. Safety of using AM in Cardiac Surgery:

The AM applied epicardially will be assesed for ease of handling and applicability, signs of hyperacute rejection (e.g., membrane changing color), and clinical indications of a problem, such as cardiac tamponade or constriction assessed throughout the hospitalization and at post-operative follow-up.

Aim 2: Compare incidence of POAF for until post-operative follow-up

The incidence and burden of POAF will be assessed using 24 hour telemetry during hospital stay as well as a daily EKG reading at home between discharge and post-operative follow-up appointment.

Aim 3: Comparison of inflammatory response: systemic and pericardial between patients who received AM and controls

The proinflammatory response to cardiopulmonary bypass circuit as measured by numerous systemic and pericardial inflammatory markers i.e. C-reactive protein (CRP), TNF-α, Interleukin (IL)-6 and brain natriuretic peptide (BNP), have been linked to induction of atrial fibrillation in a number of previous publications. Hence, these markers were chosen for our study purposes. We will collect pericardial (from chest tubes) and systemic fluid markers at pre-specified intervals. We will asses the percentage change in the levels of the biomarkers as compared to their pre-operative baseline as their will be expected variability in the level of these biomarkers at baseline.

We have assembled a strong team that combines the expertise and resources of CellReGen, the clinical knowledge of the Divisions of Cardiothoracic Surgery and Cardiovascular Medicine, and the translational depth of the Cardiovascular Research and Training Institute (CVRTI). We expect that this focused clinical trial will provide the necessary data to expand the use of AM in a large scale, extra-murally funded multi-institutional trial.

Research Design and Methods

All patients enrolled in the study will undergo the standard procedures as part of the surgical preparation and follow-up. The study is comprised of five main time periods: 1) Pre-operative screening 2) manufacturing and storage of hAM, 3) surgical application/implantation with hAM, 4) follow up and evaluation of postoperative efficacy of hAM, 5) collection and analysis of clinical data.

Preoperative screening We will enroll 40 patients undergoing elective coronary artery bypass grafting (CABG). The successfully screened cohort will be randomized to (20 patients in each arm): Interventional arm (patients who will have AM placed epicardially) and control arm (pericardial closure over great vessels and base of right ventricle, leaving the bottom part uncovered).

A pre-surgical echocardiogram will be conducted to evaluate ejection fraction, valvular dysfunction, cardiomyopathy, chamber dimensions, cardiac motion, and strain. Candidate predictor variables (patients' demographic features and clinical risk factors), echocardiographic parameters like atrial dimensions and ejection fraction, CHA_2DS_2-VASc score, and other patient factors will be collected.

Inclusion Criteria: Patients undergoing primary elective CABG at the University of Utah Hospital; Patients 18 years or older; Ability to provided informed consent and follow-up with protocol procedures

Pre-operative Exclusion Criteria: Patients in AF at the time of surgery; Prior history of sternotomy; Prior history of pericarditis; Currently on aggressive antiarrhythmic therapy (does not include beta blockers); Patients with an implantable cardiac device (pacemaker, ICD, CRT-D), ejection fraction <45%.

Patients will be randomly assigned 1:1 to the control group or the study treatment group through a computer system, REDCap, to eliminate biased treatment assignments.

Manufacturing and storage of AM: Amnion is processed from placenta that is procured from volunteer donors according to protocols approved by the Institutional Review Board at the University of Utah. The birth tissue is placed into a sterile plastic receptacle that contains 0.9% Sodium Chloride and is transported to CellReGenfor processing. The amniotic membrane is carefully separated from the chorion using blunt finger dissection. Two 2x2 cm^2 sections are cut from the amnion for sterility testing.The amnion is sent for gamma irradiation. After return of the irradiated amnion, an inspection of the product is made and the packaged membrane is stored in quarantine until the donor's medical and donor screening answers and their infectious disease testing results are reviewed and signed-off by the Medical Director, QA Specialist and Scientific Director. The customized 7x15 cm sized, rectangular shaped GMP-grade wet AM placed on Telfa gauze will be provided inside the foil pouch for this clinical trial.

Surgical application/implantation of AM: The packaged wet AM placed on Telfa gauze inside of a foil pouch, will be transferred from CellReGento the OR. At the end of planned cardiac surgery, the size and shape of customized 7x15 cm AM can be easily adjusted according to the size of the pericardium defect.

Follow-up Evaluation

a. Collection of inflammatory markers

The systemic and pericardial inflammatory markers, e.g., C-reactive protein (CRP), TNF-α, Interleukin (IL)-6 and brain natriuretic peptide (BNP), will be collected at the time of pericardiotomy. Pericardial fluid during surgery will be suctioned into a Luken trap directly from the pericardial sac. Postoperatively, the pericardial markers will be collected from the mediastinal chest tube drainage. The inflammatory markers will be collected at 24 hours, 48 hours, and 72 hours post-closing. These markers will be analyzed through ARUP.

b. Monitoring of POAF (Time frame: from discharge through surgical follow-up appointment)

The incidence of POAF would be quantified for the period between the patient's discharge and their return to clinic for the surgical post-operative follow-up appointment. Patients will be on continuous telemetry while in the hospital. They will be discharged home with a KardiaMobile EKG device, and asked to record a 6-lead EKG once daily during this period between discharge and their follow-up appointments. The number of occurrences and duration of any POAF episodes (atrial fibrillation burden) will be recorded and treated according to standard clinical practices.

c. Procedure-related serious adverse events [Time Frame: through post-operative follow-up]

Case-report forms will include collection of data for adverse events including, but not limited to, mortality, myocardial infarction, tamponade, bleeding, deep wound infection, stroke, and pericarditis. While patients will not be required to received a post-operative echocardiogram, those who do for standard of care purposes will have that data collected in the CRF.

Statistical Methods

We developed the statistical approach and determined sample size with the collaboration of Greg Stoddard, a biostatistician in the University of Utah Study Design and Biostatistics Center. We have a long history of collaborations with Stoddard.

(Aim 1). The incidence of adverse events (AEs) will be reported as percentages, with two-sided 95% confidence intervals. Statistical comparisons of AEs between the AM treatment and the control group will be made using a chi-square, or Fisher's exact test, as appropriate (based on the minumum expected cell frequencies). These statistical comparisons, however, are known to be underpowered, and so the p values will be basically just descriptive. The user experience, such as ease of handling and applicability, will be reported descriptively.

(Aims 2 and 3). Since randomization will be used, simple significance tests should be sufficient, as the need to control for confounding will be essentially eliminated. Statistical comparisons of binary outcomes will be compared using a chi-square or Fisher's exact test, as appropriate. Statistical comparisons of continous outcomes will be made using a two-sample t-test. If trends are observed in the expected direction (AM appears to be efficacous), this will support a conclusion of feasibility that justifies advancing to the next, larger study. Descriptive statistics will be reported to aid in sample size determination of the next, larger study.

Sample Size Justification

For a pilot study, where small sample sizes are used, a sample size of n = 12 per group is recommended, because the standard error of the mean is known to decrease rapidly for each additional subject up to n = 12, after which diminishing returns sets in, with each additional subject having a noticably smaller contribution to the reduction in the standard error[41]. This means that statistical power is greatly improved by increasing the sample size up to n=12, but it takes substantial increases in the sample size beyond that to impact power appreciably. For the efficacy aims (Aims 2 and 3), then, n=12 per group is sufficient to detect trends from statistical comparisons without unduly increasing the size of the study. We will use n=20 per group, however. This provides 80% power to detect a 0.80 SD difference in means, using a two-sided alpha 0.10 comparison. If the effect is large, then, we will likely see at least marginally statistical significant differences. Statistical significance is not needed, however, for a pilot feasilibity study, as only a trend in the expected direction is required. Also, the n=20 per group is large enough to provide reasonably stable estimates of means and standard deviations for sample size determination for the next, larger study. (Aim 1) The n=20 per group provides a reasonable opportunity to detect adverse events (AE) in the AM treatment group. Intuitively, if the AE is common, 1/20 or 5%, it seems that at least 20 subjects should be used to detect 1 event (1 out of 20). The exact probability is determined by the binomial probability formula,

$$\text{Prob(at least 1 event is observed | probability is 1/20)}$$
$$=1-\binom{N}{n}p^n(1-p)^{N-n} = 1-\binom{20}{0}p^0(1-p)^{20-0} = 1-(1)(1)(.95)^{20} = 1-.358$$
$$=.64 \text{ or } 64\%$$

So, if the probability of an AE is 1/20, or 5%, we will have a 64% probability of observing at least one AE in our AM treatment group. To increase the probability to 90% would require n = 45 per group, which is unreasonable. That is, it is more ethical to use fewer subjects at this stage of the product development, in case the risk of an AE is even higher. Furthermore, if the risk of the AE is very high 1/10, or 10%, we have an 88% probability of observing an AE with our n=20.

Strengths and Limitations

This is an innovative application of AM in the cardiac surgical space. Current trials for existing pericardial substitutes with biodegradable or non-biodegradable materials have been plagued with peel formation, calcification, neointima formation, inflammation, and infection.[42] These substitutes are structural barriers with no anti- inflammatory properties. Therefore, the routine clinical application of these pericardial membrane substitutes has not been achieved for a lack of reliable evidence on their beneficial impacts in clinical settings. This interdisciplinary approach presents a novel platform technology for the robust pericardium substitute with AM that significantly decreases inflammatory responses and has convenience of use due to lack of immunogenicity.

Safety issues are always a concern, yet this is a product that is already FDA-approved for tissue healing and has an excellent record at our institution. Amniotic membrane has been used as a tissue transplant since 1910. There has never been a reported disease transmission associated with AM after it has been secondarily sterilized using gamma irradiation. One of the potential complications of using hAM could be postoperative tamponade and pericardial constriction. Due to lack of immunogenicity and anti-inflammatory properties, AM has been used to decrease constrictive pericarditis.[43] AM safety in CABG patients as an epicardial substitute has been shown in a recent publication.[44]

Future Implications

This pilot project is a multidisciplinary collaboration with implications for our team and the University of Utah. This pilot project is aimed at providing an initial data and trend for the use of AM as a pericardial substitute to decrease POAF.

- Besides mitigating inflammation, AM has been shown to decreased fibrosis.[45] It is hard to quantify and characterize adhesions in clinical setting. Following a positive signal from this pilot study future animal studies looking for biochemical markers of fibrosis, devising MRI protocols to determine the severity of adhesions and quantifying adhesions at the time of re-do surgery would be undertaken. This has far reaching implications as increasing number of elderly population are undergoing re-operative surgeries and in the pediatric population, cardiac surgeons routinely perform surgery on children with previous sternotomies. Re-do sternotomy although becoming safer, is associated with increased morbidity and mortality.

- Our team is involved in a trial with CVRTI on identifying cardiac surgery patients with increased atrial substrate remodeling based on intraoperative atrial conduction characteristics recorded at time of cardiac surgery together with clinical and MRI factors to predict POAF. The intraoperative electrical mapping data utilizing a custom-made array along with clinical factors would help us to develop a real time diagnostic tool to predict POAF in cardiothoracic patients. The preliminary data from this pilot project utilizing the AM as an anti-inflammatory agent combined with our ongoing research exploring the substrate for AF, would have important therapeutic implications.

- From a commercialization standpoint, translation of positive findings to a larger scale would provide the CTRM and the University of Utah with a transformative pericardial substitute that could be applied to over 500,000 patients/year receiving heart surgery

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