Depopulated Bovine Ureteric Xenograft for Complex Haemodialysis Vascular Access

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Objectives. To assess performance of a decellularised bovine ureter vascular graft for haemodialysis in patients for whom conventional access was not possible.

Methods. The SynerGraft® Vascular Graft Model 100 (SGVG 100) is a bovine ureter modified by a tissue-engineering depopulation technology and uniquely it is not chemically cross-linked. SGVG 100 was implanted in patients with a failed fistula or vascular access grafts. Graft patency was the primary outcome; secondary outcomes included adverse events and associated treatments.

Results. 25 SGVG 100 were implanted in 23 patients; mean age was 59 ± 14 years. Mean follow-up was 370 days. The mean time to occlusion (19 events) was 215 ± 141 days with patency re-established in 14 of 18 surgical interventions. Thirty angioplasties were performed on 14 SGVG 100 for luminal/anastomotic stenosis. Two grafts demonstrated areas of dilation; however, both grafts continue to be usable at last reported follow-up (930 and 602 days) with no further changes in graft size. Primary patency, assisted primary patency, secondary patency, and freedom from infection were 29, 45, 81, and 95% at 1 year, respectively.

Conclusions. This report demonstrates SGVG 100 is a stable vascular access conduit, providing a suitable graft alternative when autologous vein is not available.

Keywords: Vascular access; Bovine ureter; Tissue engineering; Surgery; Outcome.

Introduction

The incidence of end stage renal failure treated by dialysis continues to increase in both Europe and the USA.1 Haemodialysis is the most common modality for dialysis, comprising 92% of new patients that are treated in the USA.2 The gold standard for vascular access is the creation of a primary arteriovenous fistula (AVF) using native vein. In Europe and more recently in America the benefits of this approach have been fully recognised and this approach is formalised by the DOQI guidelines in the USA.3 However, it is recognised that there will always be a percentage of patients for whom use of native vein is not possible. Hence, there is an extensive history in the use of synthetic arterio venous grafts (AVG) for this purpose. The most widely used bridge graft material for haemodialysis is polytetrafluoroethylene (PTFE).4,5 PTFE has been shown to have a wide range of primary patency rates of between 41 and 68% at 1 year.4

The main complications for PTFE grafts used for haemodialysis access have been thrombosis, reported to contribute to 70% of the failures5,7 and infection, which on average occurs in 10% of implanted PTFE grafts.5,7–9

In the past before the widespread use of synthetic grafts, biological grafts were used for vascular access and peripheral bypass surgery. Cryopreserved vascular allograft tissue has been shown to be useful in difficult vascular access situations.10,11 Cryopreserved vascular tissue is effective in cases of active infection and can be placed directly in the infected field with a low recurrence of infection.10–12

Xenografts, including natural bovine tissues (carotid artery, Artegraft® and visceral veins, Procol® and ovine collagen tubes) have been used for haemodialysis access. These grafts are traditionally treated with glutaraldehyde cross-linking to stabilise the connective tissue matrix. Reported results from clinical studies have been mixed with failures related to aneurysm formation, calcification and infection.13–19
The graft described here is unlike any other previously implanted in that it is decellularised to remove antigenicity and there is no chemical treatment allowing neo cellularisation by the host and the retention of some of the native biomechanical characteristics. To generate this graft a new method to process xenograft tissue was developed, SynerGraft® Vascular Graft Model 100 (SGVG 100, CryoLife, Inc., Kennesaw, GA, USA). The cellular elements have been removed using a proprietary SynerGraft antigen reduction technology. This technology was developed as an alternative to chemical cross-linking to render biological grafts non-immunogenic. Preliminary studies demonstrated removal of cells with retention of natural biomechanical characteristics (compliance, longitudinal and circumferential tensile strength).20

There has been no previously published data in humans using this graft for vascular access. However, in a dog arteriovenous shunt model, the primary patency of the SGVG 100 at 6 months was 72.6% (versus 58.6% for a PTFE conduits) and the 12-month patency was no different from PTFE (58.6 and 57.4%, respectively). There were no aneurysms in the SGVG 100 grafts. There were no infections among the SGVG 100 grafts, whereas three of the PTFE implants became infected with Staphylococcus intermedius (epidermidis). Migration of interstitial cells into the previously acellular matrix was ongoing as early as 2.5 months, with additional re-cellularisation and collagen biosynthetic activity observed at 1 year.21

These preclinical studies supported the application of the SGVG 100 conduit for clinical use in humans. Hence, this single centre non-randomised study was performed to review the performance of this novel biological graft.

**Materials and Methods**

The bovine ureter (SGVG 100) is obtained from cows in the USA. The graft is processed by hypotonic water lysis and incubation with DNase and RNase to destroy the cellular component, which are removed by isotonic washing over a 12-day period. The graft is gamma irradiated to sterilise it. The graft is available in 25, 35 and 50 cm lengths of approximately 0.7 cm internal diameter packed in pouches of sterile saline. The graft can be kept at room temperature with a 2-year shelf life.

**Patients**

Patients were deemed suitable for treatment with a bovine graft if multiple attempts to fashion vascular access had been made previously and attempts at

<table>
<thead>
<tr>
<th>Analysis parameter</th>
<th>SGVG 100 grafts (n=25)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ± standard deviation)</td>
<td>59.0±14.3 years</td>
</tr>
<tr>
<td>Age range (minimum to maximum)</td>
<td>35.0 to 81.0 years</td>
</tr>
<tr>
<td>Gender</td>
<td>8 male, 17 female</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>5</td>
</tr>
<tr>
<td>Hypertension</td>
<td>13</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>5</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>5</td>
</tr>
<tr>
<td>Smoking history (current or previous)</td>
<td>11</td>
</tr>
<tr>
<td>Polycystic kidneys</td>
<td>4</td>
</tr>
<tr>
<td>Chronic pyelonephritis</td>
<td>3</td>
</tr>
<tr>
<td>Previous procedures on limb (mean ± standard deviation)</td>
<td>2.4±1.0</td>
</tr>
<tr>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>3+</td>
<td>15</td>
</tr>
<tr>
<td>Years on haemodialysis (mean ± standard deviation)</td>
<td>4.2±1.6 years</td>
</tr>
<tr>
<td>0–1 year</td>
<td>2</td>
</tr>
<tr>
<td>2–3 years</td>
<td>9</td>
</tr>
<tr>
<td>4–5 years</td>
<td>7</td>
</tr>
<tr>
<td>6+ years</td>
<td>7</td>
</tr>
<tr>
<td>Indication for surgery†</td>
<td></td>
</tr>
<tr>
<td>Primary access</td>
<td>1</td>
</tr>
<tr>
<td>Failed fistula</td>
<td>21</td>
</tr>
<tr>
<td>Failed graft</td>
<td>9</td>
</tr>
<tr>
<td>Infection</td>
<td>1</td>
</tr>
</tbody>
</table>

* Twenty-five grafts implanted in 23 patients (patients with two grafts are treated as independent entries in the analysis).
† May have more than one entry per graft.
autogenous venous access was not likely to be successful (Table 1). Access in the lower limb was created only in patients with an occluded superior vena cava. No special consent was required as the product was licensed in the UK for this indication. However, a detailed patient information leaflet describing the product and any potential problems was provided and consent was taken from each patient for recording of all demographic, surgical and outcome data.

**Techniques**

All patients received their access graft under a general anaesthetic. Patients received a single dose of antibiotic prophylaxis (cefuroxime). No heparin or steroids was given. The brachial or femoral artery was prepared and clamped. An end graft to side recipient native vessel anastomosis was prepared with no undue handling and no clamping of the graft allowed. The venous site was prepared and the graft tunnelled avoiding traction injury. The graft was pulled down a hollow tunneller to achieve this. The graft was anastomosed to the vein end to side. Clamps were removed from the vein and artery and flow restored.

**Data and statistics**

The data was entered prospectively onto an online database. Outcome data was recorded, determining operative technique, primary patency, assisted primary patency and secondary patency, morbidity and mortality. Endpoints were set according to the reporting standards for arterio-venous access of the Society for Vascular Surgery and the American Association for Vascular Surgery. A data entry form was completed prospectively at the following time points, preoperatively, at the time of surgery, at each post operative follow up appointment, at the time of graft complication, at the time of color duplex assessment or flow monitoring and at patient death. Data was analysed by Kaplan–Meier statistical analysis for the calculation of overall freedom from events.

**Results**

The range of follow-up time was 44–930 days, with a mean follow-up time of 370±256 days and total follow-up time of 9247 days (25.3 patient-years). Follow-up data collection was 100% complete. Of the 25 SGVG 100 implanted, 22 went on to undergo dialysis access (one occluded day 44 and two are currently awaiting first dialysis—day 46 and day 48). The range of time to first access was 21–148 days (mean 67 days, median 55 days). Intended first needling was at 30 days but early needling occurred for total lack of alternative access. No problems were encountered in these early-needled grafts. The primary reason for delayed access in nine patients (>60 days) was limb oedema, graft needling not required or central stenosis requiring prior treatment. In this series, varying degrees of oedema or limb swelling was reported in seven grafts (two with known central vein stenosis) all seven patients with early oedema went on to undergo haemodialysis.

In these two patients fusiform dilatation (<50% increase in diameter) was seen only at needling sites and no graft was lost or revised for aneurysmal dilatation. Both grafts continue to be needled at last reported follow-up with no further changes in graft size (930 and 602 days). Distal revision with a second piece of SGVG 100 was performed in five grafts. One graft developed an anastomotic pseudoaneurysm at the arterial anastomosis and underwent an uneventful localised surgical repair. A summary of all reported complications is listed in Table 2. There were four mortalities reported in the series due to gastrointestinal bleeding at 369 days, chronic renal failure at 486 days, anoxic brain damage at 544 days and sepsis at 601 days. The deaths were not related to the SGVG 100, and all grafts were reported as patent at the time of death.

Two SGVG 100 grafts in the series developed complications related to infection. In the first, a patient developed an infection on day 587, which was initially treated with antibiotics. The graft underwent revision on day 604 to replace the infected needling site with a second SGVG 100. The old section continued to be needled and the graft remains patent at last follow-up. The second infection in a graft placed in the upper thigh, developed on day 122 and underwent a revision with a short replacement section of new SGVG 100. The surgery was initially successful, but the graft thrombosed 4 days postoperative after insertion of a tunnelled line in the ipsilateral common femoral vein and could not be saved via thrombectomy.

A total of 19 occlusions were reported in 12 SGVG 100 grafts (Table 2). The mean time to occlusion was 215±141 days (range 34–604 days). Surgery to re-establish patency was successful in 14 of 18 attempts. One patient refused exploration after the SGVG 100 graft clotted due to a hypotensive episode.

As shown in Table 3, in 19 of the 25 cases a total of 49 procedures have been required in an attempt to maintain or re-establish patency. Hence, the intervention rate to maintain or re-establish patency was 1.94
per graft year. Thirty interventional radiology pro-
cedures in 14 SGVG 100 grafts were performed to treat
luminal stenosis (Table 3). Angioplasty was the
primary treatment technique \((n \approx 30)\) with patency
re-established in all 30 procedures (four of 14 grafts
accounted for 17 procedures).

Primary patency, assisted primary patency, second-
ary patency, and freedom from infection were 29, 49,
81, and 95% at 1 year, respectively (Table 4, Fig. 1). The
event rates are shown in Table 5, demonstrating the
incidence of thrombosis to be 0.75 events per graft year
with an average of 0.76 occlusions per graft.

**Discussion**

All those responsible for vascular access surgery will
recognise a patient group in which conventional
vascular access has failed or is not possible. Previous
biological grafts have been used for this type of patient
group. These older xenografts were chemically fixed to
destroy xeno-antigenicity. However, this makes them
less biocompatible. There is also a tendency to
aneurysm formation, late aldehyde initiated calcifica-
tion and thrombosis.23,24 Graft handling and suturing
of the SGVG 100 was found to be straightforward. It is
advisable to avoid clamping the graft, excessive
traction or handling of the collagen scaffold until it
repopulates. With the graft studied there were no early
thromboses or infections (30 day) showing that the
graft is easily inserted resistant to kinking and clotting
and the patient does not require anticoagulation.

Needling for dialysis was delayed to 30 days after
insertion. This was based on the assumption that the
graft will become stronger with time as host cells
incorporate into a collagen matrix.25,26 There is
evidence from dog work21 and from grafts in this
series (data not shown) that capillaries, myocytes,
fibroblasts, neo collagen and endothelium do indeed
appear.27 In several patients needling was performed
early (14 days) after alternative access was lost. This
did not prove to be a problem and it is possible that the
graft could be needled earlier but we have no
experience of this.

The study group included patients with absence of
native vein, failed prior grafts, active infection, obesity
and central vein stenosis. The patient demographics,
time on dialysis and prior surgical attempts at access
reflect this unfavourable patient study group (Table 1).
As a consequence it is difficult to compare the results
from this series with published data using for example

**Table 2. Reported graft complications**

<table>
<thead>
<tr>
<th>Events*</th>
<th>SGVG 100 grafts</th>
<th># of grafts w/event</th>
<th>Linearised rate (events/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occlusion</td>
<td>19</td>
<td>12</td>
<td>0.75</td>
</tr>
<tr>
<td>Stenosis</td>
<td>32†</td>
<td>14</td>
<td>1.26</td>
</tr>
<tr>
<td>Dilatation</td>
<td>2</td>
<td>2</td>
<td>0.08</td>
</tr>
<tr>
<td>Infection</td>
<td>2</td>
<td>2</td>
<td>0.08</td>
</tr>
<tr>
<td>Haematoma</td>
<td>2</td>
<td>2</td>
<td>0.08</td>
</tr>
<tr>
<td>Pseudoaneurysm</td>
<td>1</td>
<td>1</td>
<td>0.04</td>
</tr>
<tr>
<td>Bleeding complication</td>
<td>1</td>
<td>1</td>
<td>0.04</td>
</tr>
<tr>
<td>Steal</td>
<td>0</td>
<td>0</td>
<td>0.00</td>
</tr>
<tr>
<td>Rupture</td>
<td>0</td>
<td>0</td>
<td>0.00</td>
</tr>
<tr>
<td>Oedema/swelling</td>
<td>7‡</td>
<td>7</td>
<td>0.28</td>
</tr>
</tbody>
</table>

* More than one complication may be reported for a single graft at follow-up.
† Six in the native vein.
‡ Two with known central vein stenosis.

**Table 3. Reported treatment procedures**

<table>
<thead>
<tr>
<th>Treatment type*</th>
<th>SGVG 100 grafts (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angioplasty</td>
<td>30</td>
</tr>
<tr>
<td>Thrombolysis</td>
<td>0</td>
</tr>
<tr>
<td>Thrombectomy</td>
<td>12†</td>
</tr>
<tr>
<td>Graft explant or ligated</td>
<td>1</td>
</tr>
<tr>
<td>Graft revision‡</td>
<td>6</td>
</tr>
</tbody>
</table>

* More than one treatment may be reported for a single graft at follow-up.
† Concomitant angioplasty and stent placement in a single graft.
‡ Five grafts with a second piece of bovine graft inserted.

**Fig. 1.** Actuarial primary and secondary patency curves at 1 year. Patency (%) ± standard error (%); solid line (primary); dashed line (secondary).
PTFE. Furthermore, we know that the threshold for the use of PTFE is much lower in the USA where most of the large studies of PTFE have been performed.28 In a large survey of PTFE in the USA, primary patency rate was 38% at 1 year and 25% at 2 years.29 PTFE was found to have a 72% secondary patency at 12 months when 70% of PTFE grafts were the first graft procedure performed.29 By comparison secondary patency for SGVG in this series was 81%, with only 4% (one of 25) of grafts places as the first access procedure. This secondary patency meets the National Kidney Foundation-Dialysis Outcomes Initiative goal of 70% at 12 months.4

One year primary patency without intervention was 29% but improved to 45% when considering grafts that were treated by angioplasty or revision without thrombosis. It had been hoped that the improved biomechanical properties of the graft might ameliorate the venous outflow stenosis seen with synthetic grafts. However, this has not been the case in these high-risk patients. Stenoses tended to occur in the distal end of the graft and not in the native vein unlike with PTFE and this made it easier to salvage. Stenoses when resected were proliferative in nature on histology (data not shown) and those treated radiologically responded readily to angioplasty.30 As a result we now assess the grafts regularly by thermodilution flow monitor initially every 3 months and perform duplex ultrasound on any graft showing decreasing flow characteristics or rising venous pressures. It would appear for the SGVG graft as with PTFE,31 that a high level of monitoring and intervention will still be required.

Infection rates have been low and it would appear that the rate is lower than historical reports on PTFE (circa 10%).5,7–9 This may well be the greatest asset for the graft. It could be postulated that the graft would have the ability to resist and remove infection. This would be supported by the low infection rates in the dog,21 in this study and when cryopreserved non cross-linked tissue was placed directly in the infected field.10–12

In conclusion, the SGVG 100 W graft may be advantageous to other biological grafts as it has wall compliance properties that may limit myo intimal hyperplasia, has a substantial wall thickness to avoid dilatation, ability to repair wall damage from needling, and ability to remove infection form needle tracts.27 Our initial experience of the SGVG 100 W shows that it was a safe and promising tool in these difficult patients. Results should improve further as less challenging patients are studied. There would now be a strong case for comparison with PTFE in a randomised trial but perhaps still concentrating on tertiary vascular access patients.

Acknowledgements

The manufactures of the bovine ureteric graft have provided the grafts at the full market price (SGVG 100, CryoLife, Inc., Kennesaw, GA, USA). Cryolife made a grant to the Department Endowment fund for research to contribute to the staff time for data collection and monitoring. An online database was set up by the Cryolife to facilitate paperless prospective data collection. All data was collected, inputted and statistics verified by the authors.

References


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