Innovative Treatment of Chronic Diabetic Foot Ulcer in a Controlled Randomized Clinical Trial Produces Fewer Adverse Events, Faster Wound Closure, and Lower Costs

Eugene J Nuccio[1]*, Lawrence A Lavery[2] and Sung-Joon Min[1]

ABSTRACT

Background: Diabetic foot ulcers (DFUs) are a common complication of diabetes. Non-healing or chronic DFUs are a growing problem associated with wound-related morbidities and high costs. Previously the treatment of chronic DFUs with a cryopreserved placental membrane (commercially known as Grafix®), in a controlled randomized clinical trial was shown to produce a significantly better clinical outcome (i.e., closed more wounds faster) compared to good wound care alone. However, associated costs with the cryopreserved placental membrane treatment has not been analyzed. The purpose of this study was to compare the estimated costs associated with good wound care versus cryopreserved placental membrane treatment in a chronic DFU randomized clinical trial.

Material and methods: Estimated costs for good wound care (control) and Grafix® (treatment) were compared for closed vs. not closed DFUs. Using empirically-based national cost estimates for treatments, medications, clinical procedures, adverse events, and serious adverse events, a series of estimated cost comparisons were computed for patients who received the treatment vs. the control. Additionally, the estimated cost of care for patients with closed vs. not closed wounds was compared.

Results: The estimated savings for the 50 treatment patients vs. 47 control patients during the trial based on only associated adverse events and serious adverse events were ~$14,000/ patient. When closed (n=41) vs. not closed wounds (n=56) were compared, the estimated costs based on treatments, medications, clinical procedures, and only associated adverse events and serious adverse events for closed wounds were also ~$14,000/patient less for the non-closed wounds.

Conclusions: The lower costs were associated with patients treated with Grafix® and were driven by fewer adverse events, fewer serious adverse events, and fewer hospitalizations due to closing wounds faster.

Abbreviations:

AE: Adverse Event; AHRQ: Agency for Healthcare Research and Quality; CMS: Centers for Medicare and Medicaid Services; DFU: Diabetic Foot Ulcer; DRG: Diagnosis Resource Group; GWC: Good Wound Care; HLT: High Level Terminology; LLT: Low Level Terminology; NARP: National Average Retail Price; RCT: Randomized Clinical Trial; SAE: Serious Adverse Event

[1]University of Colorado, Anschutz Medical Campus, USA

[2]Texas A and M University Health Science Center College of Medicine, USA

*Author for correspondence: Eugene.nuccio@ucdenver.edu

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- hypoglycemia
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- elderly

Introduction

Diabetic foot ulcers (DFUs) are prevalent and costly both to treat and to address complications, particularly those arising from infection. There are two major themes in the previous research on DFUs: 1) costs associated with DFU treatment vary widely and 2) poor or ineffective treatment will lead to utilization of more expensive and intensive services by the patient that further increase the cost of DFU care.

■ Costs of DFU treatment

Driver et al. provided a review of the literature for the DFU cost (Supplemental Table A) [1]. These authors reported that the cost of care for DFU patients is 5.4 times higher during the first year and 2.8 times higher in the second year of care compared with diabetics without foot ulcers [1]. Other researchers reported similar costs associated with the on-going treatment of DFU and/or DFU-related amputations [2-5]. Dougherty reported that the 5-year average care cost per patient with a DFU is $47,252 [2]. Margolis and colleagues reported that the average Medicare annual reimbursement for patients with DFUs increased from $31,600 in 2006 to $35,100 in 2008 [3-5]. For patients with an amputation due to DFU, reimbursement for all Medicare services increased from $49,300 to $54,100 [5]. Armstrong, Lavery, and Harkless reported that as stage and depth of DFUs increase, there is an increased risk of amputation of the affected limb [6].

In a small, blinded, randomized controlled trial (RCT) involving 35 patients in two treatment arms, Dougherty compared the cost effectiveness of an autologous platelet-rich plasma gel vs. a saline gel, and reported that the mean total cost of treatment for the former was $15,159 vs $33,214 for the latter [2]. Cost elements in this study included peer-reviewed data to simulate clinical and cost outcomes as well as QALY data. Ghatnekar et al. reported on the cost effectiveness of becaplermin, a human platelet-derived growth factor, used in the treatment of neuropathic DFUs [7].

■ Complications from poor or ineffective treatment

Edmonds identified five stages of DFUs that can lead to amputation: normal, at risk, ulcerated, infected, and necrotic [8]. The comprehensive review by Leung found that DFUs are increasing globally, and the depth of the DFU is a good prognostic measure of potential healing [9]. Lavery et al. studied the impact of foot infections and found those patients who developed a foot infection were 55.7 times more likely to be hospitalized than patients who did not develop an infection [10]. Advance stage of ulceration could lead to amputation with near-term post-operative mortality outcomes between 10-15% and three-year rates as high as 50% based on European data [11]. Wu in 2005 reported that DFUs occur in 68 per 1000 patients with diabetes per year and that more than 50% of these patients are at risk of developing an infection leading to amputation for 20% of these patients [12].

Approaches and the use of advanced wound therapies also show differential results in DFU care. Jeffcoate, Price, and Harding reported that glycaemic control, revascularization, and wound care showed promise for reversing the status of a DFU [13]. Carls and colleagues reported that podiatric physicians specializing in lower-extremity wound care can substantially reduce the overall costs associated with DFUs [14]. Cavanaugh and colleagues identified the need for a vascular surgeon to address ischaemic DFUs while noting that off-loading should always be part of the treatment [15]. Tennvall and Apelqvist using a Markov model approach whose primary outcomes were cumulative incidences of foot ulcers, amputations and deaths, costs, cost-effectiveness, and quality-adjusted life years (QALY), found that intensified prevention strategies were cost effective [16].

Comparing data from interventional and observational clinical studies from four European countries (i.e., France, Sweden, Switzerland, and the United Kingdom), they found healing rates of 47% using the becaplermin treatment vs. 35% with good wound care (GWC) with only very small differences in costs. Redekop and colleagues [17] completed an economic impact and cost effectiveness study of a bio-engineered bilayered skin substitute plus GWC compared with GWC alone in the treatment of DFUs previously reported improved healing rates (58% vs. 38%) by Veves et al. [18]. Redekop et al. used ulcer-free time, reduction of amputation risk and a Markov modeling that included a 25% chance of amputation and a 50% chance of gangrene and standardized costs associated with outpatient clinic visits, podiatrist visits, home care, hospital days, and diagnostic tests [17]. They reported slightly more ulcer-free days if the ulcer healed and slightly lower costs for both infected and uninfected ulcers for those treated with the bio-engineered skin substitute product [17]. Driver and deLeon [19] concluded that the major cost

drivers in wound care are ulceration, infection, hospitalization, and amputation—all of which can be categorized as either adverse events (AEs) or serious adverse events (SAEs) [19]. Healing DFUs quickly and efficiently using aggressive treatments makes a substantial difference in both outcomes and overall costs.

Results from a recently completed 12-week multi-center, adaptive design, single-blind, RCT of the clinical effectiveness and safety of Grafix®, the cryopreserved placental membrane for chronic DFU treatment were reported by Lavery and colleagues and are displayed in Supplemental Table B [20]. The results (N=97) demonstrated overwhelming efficacy of Grafix® (n=50; 62.0%) compared to GWC (n=47; 21.3%, p<0.0001) and showed significant reductions in median time to wound closure (42 days vs 69.5 days, p=0.019), and median number of treatments (6 vs 12, p<0.001).

The purpose of this research was to compare estimated costs for the randomized control trial reported by Lavery and colleagues [20]. Iterative methods of estimating comparative costs for the clinical trial period for both the cryopreserved placental membrane vs. GWC and the closed vs. non-closed patients are presented.

Material and Methods

There were two distinctive methodological activities associated with the results presented in the next section. First, categorical cost-related data that could be reasonably attributed to patient participation in the RCT needed to be estimated. Second, the analytic methods chosen to test the research hypotheses that the treatment utilized in the RCT a less expensive and more effective treatment than standard good practice will be presented.

■ Estimation of categorical costs

Estimates for categorical costs used in this analysis were based on standard payment tables used by national agencies such as the Centers for Medicare and Medicaid Services (CMS). There was sufficient information from the RCT data to estimate cost-of-care information for five cost-related event categories:

- Treatments—GWC vs. Grafix®, a cryopreserved placental membrane
- Medications
- Clinical procedures beyond those received during treatment
- Adverse Events
- Serious Adverse Events

■ Cost estimation for Grafix® (the cryopreserved placental membrane) treatment

One substantial difference between the actual clinical trial protocol and the estimation of costs presented here is that for the clinical trial Grafix® (the cryopreserved placental membrane) used only a 5 cm×5 cm graft regardless of the size of the DFU. However, clinical practice would use smaller grafts that more closely match the actual wound size with a progressive reduction in graft size as a wound progresses to closure. The cost estimation presented in this article matches four sizes of cryopreserved placental membrane (i.e., 5 cm×5 cm, 3 cm×4 cm, 2 cm×3 cm and 1.5 cm×2 cm) with the actual DFU size. That is, based on the clinical trial data, as the patient's DFU size decreased, the smallest available size of cryopreserved placental membrane that would completely cover the wound was matched to the DFU area. The overall product costs per patient were calculated using this approach.

■ Cost estimation for medications and procedures

For these categories national standardized data available through the Centers for Medicare and Medicaid Services (CMS) were used. The CMS National Average Retail Price (NARP) is a compilation of more the 4,600 drugs with associated dosage levels that provides the Medicaid, third party, and cash prices for these drugs. (Note: The actual patient drug costs varied widely based on the patient's specific medical plan and geographic location. However, no information regarding individual patient medical plans nor geographic location of the clinical trial site were available in the database used for these analyses. Hence, a standardized cost based on the patient's particular medication and dosage was used.) The NARP values were sorted by price per dose and average prices were derived for four levels of medication costs. Average submitted charges for outpatient procedure costs were estimated based on the number of outpatient procedures received and three levels of complexity (i.e., low, medium, high) for clinical procedures ($491.77, $1,590.98, and $2,053.82) using CMS data. Because there was no RCT information related to the severity or complexity of the outpatient clinical procedure, estimated outpatient costs

assumed that patients received an evenly distributed number of low, medium, and high cost outpatient procedures.

■ Cost estimation for AEs and SAEs

Three approaches were used to estimating costs associated with AEs and SAEs. The first approach used costs from a 2013 report by the Agency for Healthcare Research and Quality (AHRQ) on the 20 most prevalent inpatient hospital stays based on principal diagnosis and most prevalent stays for the years 1997 and 2010. Mean costs per stay for 2010 were averaged for two levels of severity and assigned for each AE cost ($9,566.67) or SAE cost ($17,210.00). This methodology, while providing a broad estimate of comparative costs, is a generalized approach and did not take into account the severity of the AE/SAEs or the length of stay associated with the particular AE/SAEs in the study.

Second, a group of clinicians, including gerontologists, reviewed the AE and SAE descriptions available in the clinical trial case report forms to determine if an AE or SAE was likely related to the treatment of the patient's DFU. The result of this refinement was to reduce the numbers of AEs and SAEs to only those associated with the patient's medical condition that was relevant to the clinical trial.

Third, a detailed review of the medical records for the AEs and SAEs was conducted to determine the most likely diagnosis resource group (DRG) that would be associated with the particular AE or SAE event. This DRG-determination process allowed the use of a CMS-generated table of costs, charges, and severity rating information for 751 DRGs based on calendar year 2013 data. Because these costs and charges were identified on a per-day basis, the length of stay information available from the RCT could now be integrated into the calculations. This DRG-based approach to estimating costs associated with AEs and SAEs provides the most accurate cost estimates for these events.

■ Analytic methods to test the research hypotheses

Using the data from the 12-week, single-blind treatment phase of the RCT, two outcome comparisons were computed. The first compared the overall costs associated with the 50 cryopreserved placental membrane patients versus the overall costs associated with the 47 GWC patients who participated in the RCT. The second comparison computed the difference in total costs between a patient with a closed DFU and the patient with a non-closed during the 12-week RCT. Both of these comparisons were tested using at two sample t-test with Satterthwaite's assumption regarding variance.

Results

■ Clinical trial outcome cost comparisons

Supplemental Table C provides a summary of the average number of applications of the cryopreserved placental membrane vs. GWC, medications, outpatient procedures, AE, and SAE events from the 12-week, single-blind phase of the clinical trial for the treatment vs. control groups and for closed vs. non-closed patients. On average, control patients had more applications, adverse events, clinical procedures, and serious adverse events when compared with cryopreserved placental membrane patients. Patients who were non-closed had higher average values on all five cost-related events when compared with closed patients. Recall that Lavery, et al. [20] also reported that cryopreserved placental membrane patients closed faster (i.e., fewer weeks on care) than those patients receiving the standard of care. Therefore, even though there is a large difference in the costs associated with standard care vs. cryopreserved placental membrane (even after adjusting for the size of the graft), because treatment patients had fewer cost-related events and fewer weeks on care during the trial, the net effect is that the overall cost of the cryopreserved placental membrane patients was expected to be lower.

■ Cost estimate #1: Matching DFU and Grafix® size

The following cost estimates are based on matching the size of the cryopreserved placental membrane product to the size of the unclosed DFU for each review event during the RCT. Each allograft was assigned a different cost based on its size. The cost estimation approaches used for medications and outpatient procedure healthcare events used average values. The estimated costs for AEs and SAEs were based on standard costs for the low level term (LLT) or high level term (HLT) available in the clinical trial coding database.

The cost estimates analysis showed that the average total estimated cost for the cryopreserved placental membrane was $32,831.93 vs. $38,344.88 for the GWC or about $5,500 (almost 17%) less. While the difference is substan-

tial, these results were not statistically significant using the Satterthwaite unequal variance t-test. If the RCT had a larger number of patients, this difference may have produced a statistically significant result. The total average estimated cost difference showed that closed patients cost approximately $20,000 less, on average, than non-closed patients ($44,220.13 non-closed vs. $23,597.70 closed) during this 12-week period. These results are statistically significant using the Satterthwaite unequal variance t-test (t=2.64; p<0.01). For every 1% improvement in healing rate there is a savings of $134.48 in the total care cost. Given that cryopreserved placental membrane produced a higher closure rate than GWC, the higher cost for the cryopreserved placental membrane is offset by the lower cost for closing the DFU.

■ Cost analysis #2: DRG costs for AEs and SAEs

Based on these very encouraging results, additional restrictions on the analyses were imposed to provide a more rigorous comparison of AE and SAE costs identified during this phase of the RCT. The same restrictions were tested for treatment vs. control and closed vs. non-closed patients, including:

- Specifying AE and SAE costs and/or charges based on the DRG characterization of these events rather than the low level terminology (LLT) or high level terminology (HLT) values reported previously.
- Characterizing the AE and SAE events as likely related to the DFU clinical trial activity (e.g., abrasion of Right Great Toe) vs. unlikely to be related to the DFU clinical trial activity (e.g., abdominal cramping).
- Accounting for the number of hospital days of stay for each SAE event rather than an average cost per event.

After completing a clinical review of the available medical records for SAEs and corroborating the information from the available clinical trial data, there was a substantial difference in the average number of hospital stay days between the cryopreserved placental membrane and GWC patients. GWC patients' hospital stays averaged nearly 2.5 times longer than cryopreserved placental membrane patients (12.7 days vs. 5.2 days, respectively). Additionally, the GWC patients totaled nearly 50% more SAEs than for the cryopreserved placental membrane patients (17 SAEs vs. 13 SAEs, respectively). Both of these elements added to the overall increases in costs for the cryopreserved placental membrane vs. GWC comparison, as well as the comparison between those patients whose DFU closed vs. did not close.

The estimated costs controlled for three additional sources of variability (i.e., basing average costs for the hospitalization on the probable DRG; restricting estimated costs to only related AEs/SAEs; and accounting for differential costs due to length of stay). This provided the most rigorous cost estimates given the data available from the RCT. As with the previous analyses, two sets of estimated costs, one for cryopreserved placental membrane vs. GWC and a second for patients who had closed vs. non-closed DFUs were computed.

■ Differential total cost comparisons

TABLE 1 shows that there are substantial differences that favor the cryopreserved placental membrane and closed patients in total costs when either all or only related AEs/SAEs were included in the computation. The total costs using DRG-based and length of stay information for all AEs/SAEs showed that the average total cost was nearly $19,000 less for cryopreserved placental membrane vs. GWC patients ($52,931.72 vs. $34,039.79). The net average savings was slightly less (~$15,000) when the analyses were restricted to AEs/SAEs that were likely related to DFUs ($42,347.32 vs. $27,534.45, respectively).

Discussion and Limitations

Because there was no patient-level cost data collected in the initial clinical protocol, all analy-

Table 1: Costs for All vs. Only Related AE and SAE Events for Cryopreserved Placental Membrane (Grafix®) vs. Good Wound Care (GWC) Patients.

	DRG Ave Costs	
Comparison Groups	**All AE/SAE**	**Only Related AE/SAE**
Grafix® (n=50)	$34,039.79	$27,534.45
GWC (n=47)	$52,931.72	$42,347.32
p-value	0.067	0.082

Table 2: Costs for All vs. Only Related AE and SAE Events for Closed vs. Not Closed Patients.

	DRG Ave Costs	
Comparison Groups	**All AE/SAE**	**Only Related AE/SAE**
DFU Closed (n=41)	$31,628.82	$26,728.82
DFU Not Closed (n=56)	$51,660.68	$40,556.51
p-value	0.048	0.09

Table 2 shows very similar results when estimated costs for patients with closed vs. non-closed DFUs are compared. The total costs using DRG-based and length of stay information for all AEs/SAEs showed that the average total cost was $20,000, whereas the average total cost between closed vs. non-closed DFUs using only AEs/SAEs produced a nearly $14,000 lower cost for closed than not closed DFU.

ses are based on estimates of the costs associated with closing DFUs. The five cost elements (i.e., treatments, medications, outpatient procedures, adverse events, and serious adverse events), while scientifically defensible, does make a number of assumptions about how costs are distributed that may not reflect the actual experiences of DFU patients. While the DRG analyses do provide cost estimates using severity indicator values and account for different LOS values, the DRGs are based on retrospective review of the patient's clinical record rather than by the actual DRG generated by the patient's actual claim. Medication cost estimates could be refined by matching at the patient levels the medication names, dosage level, and dosage frequency to actual costs by each patient.

These limitations aside, the results show that using a matched-size graft produced lower average estimated costs for the patients receiving the cryopreserved placental membrane based on the best clinical information and strongly empirically grounded cost estimation methods based on data from an RCT for DFUs.

Conclusion

The results from the 12-week, multi-center, adaptive design, single-blind, RCT support the conclusion that the cryopreserved placental membrane was superior to GWC both in its clinical effectiveness with a 62.0% vs. 21.3% healing rate ($p<0.0001$) and estimated associated costs. As the methodologies used to estimate costs and charges associated with the treatment were refined to increase the predictive accuracy of these costs, the total estimated cost differences between cryopreserved placental membrane and GWC patients was typically statistically significant at $p<0.05$ and were substantial, ranging from $15,000 and $19,000. The analyses of average estimated total costs for patients whose DFU closed vs. those patients whose DFU did not close produce very similar cost differences favoring the cryopreserved placental membrane.

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