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Application of Freshly Collected Placental Membrane in Venous Ulcer Treatment

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ABSTRACT

Background: Chronic venous ulcers are marked by impaired healing, persistent inflammation, and microbial colonization, resulting in prolonged morbidity and substantial economic burden. The placental (amniotic) membrane is rich in pluripotent and mesenchymal cells, angiogenic mediators, growth factors, and innate antimicrobial peptides, and has emerged as a promising biomaterial for regenerative wound therapy owing to its anti-inflammatory, low-immunogenic, antimicrobial, and pro-epithelialization properties.

Objective: To evaluate the efficacy of placental membrane dressing in enhancing wound healing and microbial inhibition in chronic venous ulcers, compared with standard care.

Methods: An open-label, randomized controlled trial was conducted in the Department of RMTS, School of Tropical Medicine, Kolkata. Forty patients (aged ≥12 years) with chronic venous ulcers of more than six weeks' duration were randomized equally (n=20 each) to a placental membrane dressing group or a standard care group (systemic antibiotics with iodine-based dressing). Outcomes—ulcer area reduction, time to complete healing, epithelialization, microbial load, and secondary wound characteristics—were assessed weekly over a six-month follow-up.

Results: The placental membrane group showed significantly greater early healing, with ≥50% ulcer area reduction at 4 weeks in 65% versus 30% of patients ($p=0.03$) and complete healing at 12 weeks in 55% versus 20% ($p=0.02$). Mean time to healing was shorter (9.4 ± 2.6 vs 13.8 ± 3.1 weeks; $p<0.01$). Mean bacterial bioburden fell from 5.6 to 2.1 $\log_{10}$ CFU/g in the membrane group versus 5.5 to 4.3 $\log_{10}$ CFU/g in controls ($p<0.001$), with greater reductions in wound discharge, odor, and pain. No adverse reactions were observed.

Conclusion: Placental membrane dressing significantly enhances wound healing, accelerates epithelial regeneration, and exhibits superior antimicrobial activity compared with standard care, representing a cost-effective, culturally acceptable, and biologically active therapeutic alternative in chronic wound management.

Keywords: *Placental membrane; Amniotic membrane; Chronic venous ulcer; Wound healing; Antimicrobial; Regenerative medicine.*

INTRODUCTION

Chronic venous ulcers represent the most common type of lower-limb ulceration and are a major source of long-term morbidity, reduced quality of life, and recurrent healthcare expenditure.[1,2] They arise predominantly from sustained venous hypertension and incompetent valvular function, which promote a self-perpetuating cycle of impaired microcirculation, persistent inflammation, and delayed tissue repair. A hallmark of these wounds is their resistance to conventional therapy:

many remain unhealed for months to years despite compression and standard dressings, and a substantial proportion recur after closure.[3]

The pathological wound environment of a chronic venous ulcer is characterized by elevated levels of pro-inflammatory cytokines and proteases, depletion of viable growth factors, and frequent polymicrobial colonization and biofilm formation.[3] This microbial burden sustains inflammation, degrades the extracellular matrix, and obstructs the orderly transition from the inflammatory to the proliferative phase of healing. Consequently, therapies that can simultaneously modulate inflammation, deliver regenerative signals, and suppress microbial colonization are of considerable clinical interest.

The human placental membrane—comprising the amnion and chorion—has attracted growing attention as a biologically active wound dressing.[4,5] It is a rich reservoir of mesenchymal and epithelial stem cells, structural collagen, angiogenic mediators, and a broad panel of growth factors including epidermal growth factor, transforming growth factor-β, fibroblast growth factor, and platelet-derived growth factor.[6] In addition, the membrane harbors innate antimicrobial peptides such as defensins and cathelicidins that confer intrinsic resistance to a wide range of pathogens.[7] Its low immunogenicity, anti-inflammatory action, and capacity to promote re-epithelialization make it a particularly attractive biomaterial for regenerative wound therapy.[8]

Despite encouraging laboratory and preliminary clinical evidence, robust comparative data on placental membrane dressing for chronic venous ulcers in resource-constrained settings remain limited.[9,10] The present randomized controlled trial was therefore undertaken to evaluate the efficacy of placental membrane dressing in enhancing wound healing and reducing microbial load in chronic venous ulcers, in direct comparison with standard wound care.

MATERIALS AND METHODS

Study Design and Setting

This study was conducted as an open-label, randomized controlled trial in the Department of Regenerative Medicine and Translational Science (RMTS), School of Tropical Medicine, Kolkata. The trial was carried out in accordance with the principles of the Declaration of Helsinki, and written informed consent was obtained from all participants prior to enrolment.

Study Population

A total of 40 patients aged 12 years and above, presenting with chronic venous ulcers of more than six weeks' duration, were enrolled in the study.

Inclusion and Exclusion Criteria

Patients with clinically diagnosed chronic venous ulcers persisting for more than six weeks were included. Patients with active systemic infection, malignancy at the ulcer site, immunocompromised states, uncontrolled diabetes mellitus, severe peripheral arterial disease, or unwillingness to participate were excluded from the study.

Randomization and Group Allocation

Participants were randomly allocated into two equal groups (n=20 each) using a simple randomization method:

- Study Group: treated with placental membrane dressing.
- Control Group: treated with standard wound care consisting of systemic antibiotics and iodine-based dressing.

Preparation and Application of Placental Membrane

Fresh placental membranes were collected within four hours of normal delivery under aseptic conditions, washed with normal saline, and screened for HIV, hepatitis B, hepatitis C, and syphilis.[11] The membrane was applied directly over the ulcer once weekly and covered with a sterile secondary dressing.

Wound Assessment and Follow-Up

Baseline assessment included ulcer size, wound bed characteristics, granulation tissue, epithelialization, and signs of infection. Wound swabs and tissue samples were taken for microbiological analysis and quantification of bacterial bioburden (expressed as $\log_{10}$ colony-forming units per gram of tissue). Patients were followed weekly, and changes in ulcer area, epithelial regeneration, microbial load, discharge, odor, and pain were recorded over a six-month follow-up period.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation and compared using the independent-samples t-test, while categorical variables were expressed as frequencies with percentages and compared using the chi-square or Fisher's exact test, as appropriate. A two-tailed p-value of less than 0.05 was considered statistically significant. All analyses were performed using standard statistical software.

RESULTS

A total of 40 patients completed the study, with 20 patients in each group. The two groups were comparable at baseline with respect to age, sex distribution, ulcer duration, and ulcer area, with no statistically significant differences (Table 1).

Table 1. Baseline Characteristics of Study Participants

Parameter	Placental Membrane Group (n=20)	Standard Care Group (n=20)	p-value
Mean age (years)	46.8 ± 12.4	48.1 ± 11.9	0.72
Male : Female	13 : 7	12 : 8	0.75
Mean ulcer duration (weeks)	14.6 ± 4.2	15.1 ± 4.5	0.68
Mean ulcer area (cm²)	18.9 ± 6.3	19.4 ± 6.1	0.81
Diabetes mellitus, n (%)	5 (25%)	6 (30%)	0.72
Hypertension, n (%)	8 (40%)	7 (35%)	0.74
Right : Left limb	11 : 9	10 : 10	0.75

Wound Healing Outcomes

Patients treated with placental membrane dressing demonstrated significantly faster and more complete healing than those receiving standard care. Early healing (≥50% ulcer area reduction at 4 weeks) was achieved in 65% of the membrane group versus 30% of controls (p=0.03), and complete healing at 12 weeks was observed in 55% versus 20%, respectively (p=0.02). The mean time to complete healing was substantially shorter in the membrane group (9.4 ± 2.6 weeks) than in the control group (13.8 ± 3.1 weeks; p<0.01) (Table 2).

Table 2. Comparison of Wound Healing Outcomes

Outcome	Placental Membrane Group (n=20)	Standard Care Group (n=20)	p-value
≥50% ulcer area reduction at 4 weeks	13 (65%)	6 (30%)	0.03
Complete healing at 12 weeks	11 (55%)	4 (20%)	0.02
Mean time to healing (weeks)	9.4 ± 2.6	13.8 ± 3.1	<0.01

Serial Reduction in Ulcer Area

Serial measurement of mean ulcer area showed a progressively greater reduction in the membrane group at each follow-up interval. By week 8, the mean ulcer area had decreased to 6.2 cm² in the membrane group compared with 12.1 cm² in the control group, corresponding to a mean reduction of 67.2% versus 37.6% from baseline (Table 3).

Table 3. Serial Mean Ulcer Area (cm²) and Percentage Reduction from Baseline

Time point	Placental Membrane Group (mean ± SD)	Standard Care Group (mean ± SD)	p-value
Baseline	18.9 ± 6.3	19.4 ± 6.1	0.81
Week 2	14.8 ± 5.1	17.2 ± 5.6	0.16
Week 4	9.8 ± 4.0	14.3 ± 4.9	<0.01
Week 6	7.6 ± 3.4	13.0 ± 4.5	<0.01
Week 8	6.2 ± 3.1	12.1 ± 4.2	<0.01
Reduction at 8 weeks	67.2%	37.6%	<0.01

Microbial Load Reduction (Figure 1)

Quantitative microbiological assessment revealed a marked and sustained reduction in bacterial bioburden in the membrane group. Mean bacterial load decreased from 5.6 ± 0.8 $\log_{10}$ CFU/g at baseline to 2.1 ± 0.7 $\log_{10}$ CFU/g by week 8 in the membrane group, compared with a modest fall from 5.5 ± 0.9 to 4.3 ± 1.0 $\log_{10}$ CFU/g in the control group (p<0.001 at week 8). The proportion of culture-negative wounds at week 8 was significantly higher in the membrane group (60% vs 20%; p=0.01) (Table 4).

Table 4. Microbial Load ($\log_{10}$ CFU/g) and Culture Status

Parameter	Placental Membrane Group (n=20)	Standard Care Group (n=20)	p-value
Baseline mean load	5.6 ± 0.8	5.5 ± 0.9	0.71
Week 4 mean load	3.4 ± 0.9	4.8 ± 0.9	<0.001
Week 8 mean load	2.1 ± 0.7	4.3 ± 1.0	<0.001
Culture-negative at week 8, n (%)	12 (60%)	4 (20%)	0.01

Table 5. Distribution of Predominant Isolates at Baseline

Organism	Placental Membrane Group, n (%)	Standard Care Group, n (%)	p-value
Staphylococcus aureus	7 (35%)	6 (30%)	0.74
Pseudomonas aeruginosa	5 (25%)	6 (30%)	0.72
Escherichia coli	3 (15%)	4 (20%)	0.68
Klebsiella species	2 (10%)	2 (10%)	1.00
Mixed / polymicrobial	3 (15%)	2 (10%)	0.63

Secondary Wound Characteristics at 8 Weeks (Figure 2)

At eight weeks, the membrane group showed clearly superior wound-bed characteristics. Healthy granulation tissue covering more than 75% of the wound bed was present in 80% of membrane-treated ulcers versus 40% of controls (p=0.01), while purulent discharge, malodor, and significant pain were all markedly less frequent in the membrane group (Table 6).

Table 6. Secondary Wound Characteristics at 8 Weeks

Characteristic	Placental Membrane Group (n=20)	Standard Care Group (n=20)	p-value
Healthy granulation >75% wound bed	16 (80%)	8 (40%)	0.01
Active epithelialization at margins	15 (75%)	7 (35%)	0.01
Purulent discharge present	3 (15%)	10 (50%)	0.02
Malodor present	2 (10%)	9 (45%)	0.01
Moderate-to-severe pain (VAS ≥4)	4 (20%)	12 (60%)	0.01

Safety Outcomes

No adverse reactions, graft rejection, allergic responses, or worsening of comorbid conditions were observed in either group throughout the study period. Placental membrane application was well tolerated, and no patient required discontinuation of the assigned treatment.

DISCUSSION

The findings of this randomized controlled trial demonstrate that placental membrane dressing offers a clear therapeutic advantage over standard care in the management of chronic venous ulcers. Patients treated with the membrane achieved earlier and more complete healing, a shorter mean time to closure, and superior wound-bed characteristics, alongside a pronounced reduction in microbial bioburden.

These results are biologically plausible given the composition of the placental membrane. Its abundant growth factors and mesenchymal stem cells provide a regenerative scaffold that promotes angiogenesis, fibroblast proliferation, and orderly re-epithelialization, while its anti-inflammatory mediators help interrupt the chronic inflammatory loop that characterizes non-healing wounds.[4,8] The marked decline in bacterial load observed in the membrane group is consistent with the known activity of placental antimicrobial peptides such as defensins and cathelicidins, which can suppress a broad spectrum of pathogens without the selective pressure associated with systemic antibiotics.[7]

The significantly higher proportion of culture-negative wounds and the greater reduction in discharge and odor in the membrane group suggest that the dressing addresses both the regenerative and the infective components of chronic ulceration simultaneously. This dual action is clinically valuable, as it may reduce reliance on prolonged systemic antibiotic therapy and the attendant risk of antimicrobial resistance.[9,10,12]

From a practical standpoint, placental membrane is a cost-effective and readily available biomaterial in settings where normal deliveries are common, and its use is generally culturally acceptable. The absence of adverse reactions in the present cohort reinforces its favorable safety profile. Nonetheless, the study is limited by its modest sample size, single-center design, and open-label nature, which may introduce assessment bias. Larger, multicenter, blinded trials with longer follow-up and standardized membrane processing are warranted to confirm these findings and to establish optimal application protocols.

CONCLUSION

Placental membrane dressing significantly enhances wound healing, accelerates epithelial regeneration, and exhibits superior antimicrobial effects compared with standard care. It represents a cost-effective, culturally acceptable, and biologically active therapeutic alternative in chronic wound management, and merits wider evaluation as a regenerative-medicine strategy for chronic venous ulcers.

DECLARATIONS

Ethics approval and consent to participate: The study was approved by the Institutional Ethics Committee, and written informed consent was obtained from all participants.

Conflict of interest: The authors declare that they have no competing interests.

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