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CLINICAL RESEARCH

Guided tissue regeneration with a gelatin and polycaprolactone composite membrane for repairing oral soft tissue defects: A prospective, single-blinded, randomized trial

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ABSTRACT

Statement of problem. Clinical trials comparing outcomes of the guided tissue regeneration membrane (TRM), fabricated from gelatin and polycaprolactone via electronspinning technology, with collagen membrane for repairing oral soft tissue defects are lacking.

Purpose. The purpose of this clinical trial was to evaluate the efficacy and safety of TRM compared with collagen membrane in reconstructing oral soft tissue defects.

Material and methods. This prospective, single-blinded, randomized, noninferiority trial involved 48 participants with oral lesions who were randomized (1:1) into 2 groups: surgery + TRM or surgery + collagen membrane. The primary endpoint was to establish a noninferiority margin of −10% regarding Grade A healing rates 1 month ±7 days after surgery between groups. Secondary endpoints included instrument performance, Grade A healing rate at 10 ±3 days and 3 months ±7 days after surgery, time to achieve Grade A healing, surgical area satisfaction and wound contraction at 10 ±3 days, 1 month ±7 days, and 3 months ±7 days after surgery. Adverse events were assessed to evaluate the safety of TRM. The independent samples *t* test was used for continuous variables between groups, and the Fisher exact test or chi-squared test was used for categorical variables (α=.05).

Results. The Grade A healing rate was 100% in both groups at 1 month ±7 days after surgery in the full-analysis and per-protocol sets. The 95% confidence interval of the rate difference (0%) was −5% to +5%, within the predefined noninferiority margin of −10%, indicating that TRM was not inferior to collagen membrane. No significant differences in secondary endpoints were found between groups (*P*>.05). Adverse events rates were also similar between groups (serious adverse events: 3 [12.50%] for TRM and 1 [4.17%] for collagen membrane, *P*=.609; overall adverse events: 7 [29.17%] for TRM and 4 [16.67%] for collagen membrane, *P*=.303).

Conclusions. TRM demonstrated noninferiority to collagen membrane for reconstructing oral soft tissue defects. (J Prosthet Dent 2025;133:1221-1228)

Oral soft tissue defects are often caused by trauma, the surgical excision of oral mucosal diseases, or tumors. Given the complex anatomy of the oral cavity, reconstruction requires not only defect repair but also functional restoration. Traditional repair methods rely on autografts, and, although they have achieved a certain level of success, the main drawbacks include donor site morbidity and technical challenges.[1] Platelet-rich plasma is also used to cover defects but is costly, difficult to use widely, and time consuming to produce.[2]

Acellular dermal matrix (ADM) is a synthetic material without risk of immune rejection, which preserves the structure and function of the dermal matrix. ADM serves as a 3-dimensional (3D) tissue scaffold that promotes the proliferation and differentiation of epithelial cells and fibroblasts.[3] Among ADM materials, collagen membrane, such as the Heal-All membrane (Yantai Zhenghai

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Clinical Implications

Traditional methods of repairing oral soft tissue defects have limitations. Advances in electrospinning materials present new avenues for repair. However, comprehensive trials demonstrating the efficacy and safety of electrospinning materials remain absent. Further research should be conducted to confirm the applicability of these materials for oral soft tissue repair.

Bio-Tech Co, Ltd.), has shown success in soft tissue repair.[4–7] The Heal-All membrane decellularizes bovine-derived tissues and produces a bilayer scaffold with a natural tissue spatial structure which guides the binding of soft, hard, and vascular endogenous tissues to the membrane. Zhu et al[8] reported that the Heal-All membrane has a homogeneous and dense structure, providing 3D stability for tissue regeneration. However, its dense structure may restrict appropriate pore diameter, which may affect fibroblast activities. Furthermore, the loose arrangement of collagen fiber bundles and rapid degradation rate may compromise space maintenance,[9] raising concerns over mechanical strength,[10] potentially leading to postoperative collapse, swelling, and other complications that compromise its clinical effect.[11,12] Developing a new commercially available membrane with suitable properties is urgent, as the repair of oral soft tissue defects continues to face major challenges.

Electrospinning materials, because of their ability to mimic the extracellular matrix (ECM), offer advantages such as larger pore diameters and an increased surface area-to-volume ratio (SA/V)[13] and have been successfully applied to the repair of various tissues, including skin,[14] bone,[15] blood vessels,[14] and nerves.[16] Extensive research on prospective applications in drug delivery,[14] wound healing,[17] and other fields has been conducted. Electrospinning materials can embed drugs into fibers, facilitating sustained drug release[18] and effectively promoting the healing process. This is particularly important for the repair of soft tissue defects.[18]

The tissue regeneration membrane (TRM) is a nanoscale gradient layer bioscaffold material composed of polycaprolactone (PCL) and gelatin (Gel) made using electrospinning technology. PCL is a synthetic biopolymer with excellent mechanical properties, but it lacks bioactive components and degrades slowly. Natural polymer gel has excellent water solubility, degradability, and the biocompatibility required for cell attachment and biological activities such as cell differentiation, proliferation, and executive functions.[19] Thus, TRM has been considered to have optimal characteristics[20,21] and is expected to overcome the limitations of existing materials.

Comparative data on the efficacy and safety of electrospinning membranes and collagen membrane are unclear. This study aimed to evaluate the efficacy and safety of TRM against the Heal-All membrane for the repair of oral soft tissue defects. The null hypothesis was that the lower limit of the 95% confidence interval (CI) of the rate difference between the TRM group and the Heal-All membrane group would exceed −10%.

MATERIAL AND METHODS

The study was approved by the Medical Ethics Committee of the First Affiliated Hospital of Chongqing Medical University on May 10, 2021 (number CY20213701) and was registered in the Chinese Clinical Trial Registry (number ChiCTR2400086999). The trial was undertaken according to good clinical trial management practice for medical devices and the Declaration of Helsinki Protocol (and any modifications thereof). All participants provided written informed consent before the trial. The study inclusion and exclusion criteria are presented in Table 1.

The sample size was determined according to the primary endpoint. According to the data of the Grade A healing rate of similar surgeries in our department in the past 5 years, it was assumed that the Grade A healing rate of both the trial and control group would be 99.00%, with a noninferiority margin of −10%, α =.05 (bilateral), 1-β =.8, Pt and Pc, respectively, were Grade A healing rates of trial group and control group. The sample size formula was: $N = (Z1 - \alpha/2 + Z1 - \beta)^2[Pc(1 - Pc) + Pt(1 - Pt)]/[|Pt - Pc| - (-10\%)]^2$, and the sample size of each group was calculated as 16 participants. Considering a dropout rate of 20%, the sample size was increased to 24 participants for each group.

The participants were randomly assigned (1:1) using a random number table generated using the blocked randomization of a macroprogram (SAS Institute) after the resection of the lesions. The trial group received TRM (Neomodulus Medical Sci-Tech Co, Ltd.), while the control group received the Heal-All membrane (Yantai Zhenghai Bio-Tech Co, Ltd.). This trial used a single-blinded design, wherein the participants were masked to the treatment but not the clinicians.

Following the resection of the lesions, hemostatic debridement was performed, and the maximum and minimum diameters of defects were recorded using a ruler. TRM was trimmed to the appropriate size and positioned over the defect with the edges of the membrane extending by approximately 2 to 3 mm outside the defect to ensure margin closure. An iodoform gauze was placed on the surface using a 3–0 absorbable suture after

Table 1. Study inclusion and exclusion criteria

Inclusion criteria	Patients aged 18–70 years
	oral soft tissue defects resulting from various etiologies including but not limited to: surgical excision of benign and malignant tumors (such as, pleomorphic adenoma, fibromas, squamous cell carcinoma), oral mucosal diseases leading to significant tissue loss necessitating repair including chronic ulcers or leukoplakia
	Defect sizes ranging from 1.5 cm^2 to 20 cm^2 as measured by operator using ruler
	Patients can tolerate surgery
	Patients voluntarily participated in this trial and signed informed consent form.
Exclusion criteria	Patients with diabetes (fasting blood glucose [FBG] ≥8.8 mmol/L or 2-h postprandial blood glucose [2 h PBG]≥11.1 mmol/L)
	Patients with acute infection of defect area or whole body
	Patients with liver and kidney insufficiency (aspartate aminotransferase [AST], alanine aminotransferase [ALT], creatinine>2 times normal values)
	Those with abnormal coagulation mechanism (prothrombin time [PT], activated partial thromboplatin time [APTT]>2 times the normal values)
	Pregnant or lactating women
	Patients with history of preoperative radiotherapy or chemotherapy within 6 months before surgery
	Patients with autoimmune disease
	Those who cannot accept bovine-derived materials
	Patients with surgical contraindications
	Alcohol or drug abusers
	Patients with hypoproteinemia (serum albumin < 30g/L) or cachexia
	Patients attended other clinical trials within 1 month before surgery
	Patients considered unsuitable for inclusion by investigator.

the membrane had been attached to the tissue, and the appropriate pressure was applied for reverse dressing and fixation, as shown in Figure 1A-C.

The process for the Heal-All membrane was similar to that of TRM as shown in Figure 1D-F. However, the Heal-All membrane must be hydrated in sterile stroke-physiological saline solution before trimming. Additionally, it features a smooth (up) and a rough side (down), the "up" side must face outward while covering the defect. In contrast, the “up” side of TRM does not need to be distinguished. The whole procedure was performed by the same team member (H.T.). Photographs were recorded throughout the entire procedure (including the location and number of defects).

Follow-ups were set at 10 ±3 days, 1 month ±7 days, and 3 months ±7 days after surgery to assess the Grade A healing rate, instrument performance, time to Grade A healing, surgical area satisfaction, wound contraction, and occurrence of adverse events (AEs) and serious adverse events (SAEs), and the surgical areas were photographed.

A third-party investigator (T.W.) blinded to group information conducted efficacy assessments. The

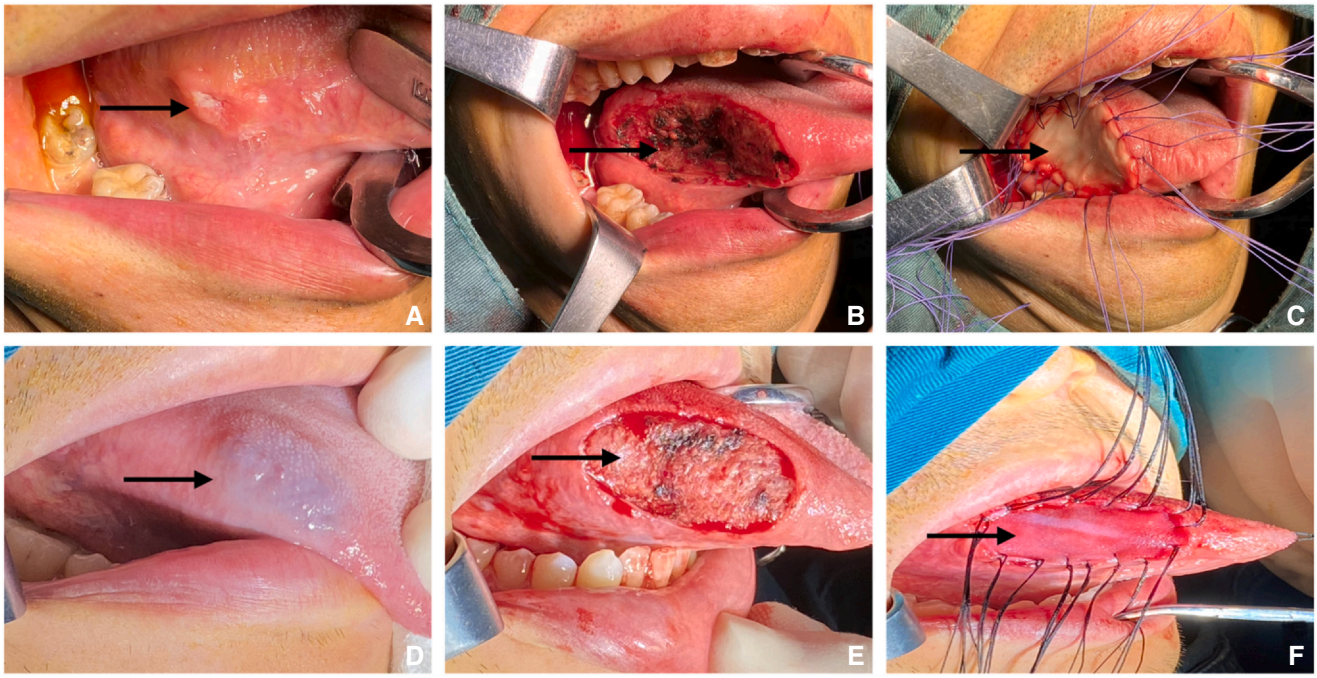

Figure 1. Surgical procedure for tongue lesions. A, Preoperative images displaying tongue lesions in trial group. B, Defects resulting from excision of tongue lesions in trial group. C, Trial group received TRM application. D, Preoperative images displaying tongue lesions in control group. E, Defects resulting from excision of tongue lesions in control group. F, Control group received Heal-All membrane application.

Table 2. Grade of healing in surgical areas

Outcome	Evaluation Criteria
Grade A Healing	Excellent healing without adverse reactions such as redness, exudation, or infection.
Grade B Healing	Poor wound healing accompanied by signs of inflammation such as redness, induration, and serous exudation, but without purulent symptoms.
Grade C Healing	Purulent symptoms present, requiring surgical incision and drainage.

evaluation criteria were divided into 1 primary endpoint, 5 secondary endpoints, and 4 safety endpoints. The primary endpoint was the Grade A healing rate at 1 month ±7 days after surgery. Currently, there is no consensus regarding a criterion standard for Grade A healing.[22] Epithelialization typically occurs within 2 to 3 weeks after surgery. Complete epithelialization takes about 1 month[23] and usually no redness, swelling, exudation, or infection, is observed visually. It was calculated as follows: (number of Grade A healing participants/total number of participants)×100%, with specific criteria detailed in Table 2.

The 5 secondary endpoints were Grade A healing rates assessed at 10 ±3 days and 3 months ±7 days after surgery; instrument performance based on the ease of incision, suturing, and attachment; time to achieve Grade A healing; surgical area satisfaction and wound contraction evaluated at 10 ±3 days, 1 month ±7 days, and 3 months ±7 days after surgery. The evaluation criteria for surgical area satisfaction and wound contraction are shown in Table 3. Four safety endpoints were AEs and SAEs; complications including allergic reactions, infections, dysplasia, hyperkeratosis, ulcers, and compromised nerve and vascular protection; instrument defects such as labeling errors, quality issues, and malfunctions; laboratory examinations.

The primary endpoint adopted a noninferiority trial with a noninferiority margin of −10%. Noninferiority was established when the lower limit of the 95% CI of the rate difference between the TRM group and the Heal-All membrane group exceeded −10%. Primary and secondary endpoints analyses were performed in the full-analysis sets (FASs) and per-protocol sets (PPSs). Safety endpoints were evaluated in all participants who underwent randomization. For the primary endpoint in FAS, the worst observation was carried forward using the imputation method to address missing data by utilizing the worst observation outcome from all visits to fill the missing data.

The data were analyzed using a statistical software program (IBM SPSS Statistics for Windows, v27.0; IBM Corp). Continuous variables were presented as mean ±standard deviations, nonnormal distribution variables are reported as medians (Q1, Q3), and categorical variables were reported as numbers and percentages. The Student *t* test was used to compare continuous variables between groups, and the Fisher exact test or chi-squared test, as appropriate, was used for categorical variables. All statistical tests were 2-sided (α=.05).

RESULTS

Between September 2021 and February 2023, 49 participants were recruited, of which 48 were randomized (1 declined to participate); 24 were allocated to the TRM group, and 24 to Heal-All membrane group. Overall, the FAS included 48 participants (24 in TRM and 24 in Heal-All membrane), and the PPS included 46 participants (23 in TRM and 23 in Heal-All membrane). Details are presented in Figure 2. The 2 groups were well balanced in baseline demographics as shown in Table 4.

At 10 ±3 days after surgery, the Grade A healing rate was 0% for both the TRM and Heal-All membrane groups, as shown in Figures 3A and 3B, indicating a lack of epithelial migration.

The Grade A healing rate reached 100% at 1 month ±7 days after surgery for both the TRM and Heal-All membrane groups in FAS and PPS, as shown in Figures 3C and 3D, respectively. The 95% CI of the rate difference was 0%, (−5% to +5%) according to the Fisher exact test, within the predefined noninferiority margin of −10%, confirming noninferiority of TRM.

By 3 months ±7 days after surgery, the Grade A healing rate was 100% in both the TRM and Heal-All membrane groups, as shown in Figures 3E and 3F.

Table 3. Evaluation of surgical area satisfaction and wound contraction

	Outcome	Evaluation Criteria
Surgical Area Satisfaction	Satisfied	Repaired area has normal or pink mucosal color, with elasticity, soft texture, no tissue reaction or discomfort, is esthetically pleasing, and high level of comfort.
	Average	Repaired area has milky white color, moderate elasticity, tough texture, slight tissue reaction and discomfort, average esthetics, and mild comfort level.
	Unsatisfied	Repaired area has gray-white color, no elasticity, hard texture, severe tissue reaction and discomfort, unappealing esthetics, and poor comfort.
Wound Contraction	Normal	Normal epithelial proliferation without contraction, soft texture, does not affect normal oral function.
	Moderate Contraction	Localized contraction of wound, relatively hard texture, affecting normal oral function.
	Severe contraction	Extensive contraction of wound, hard texture, extremely affecting normal oral function or loss of function.

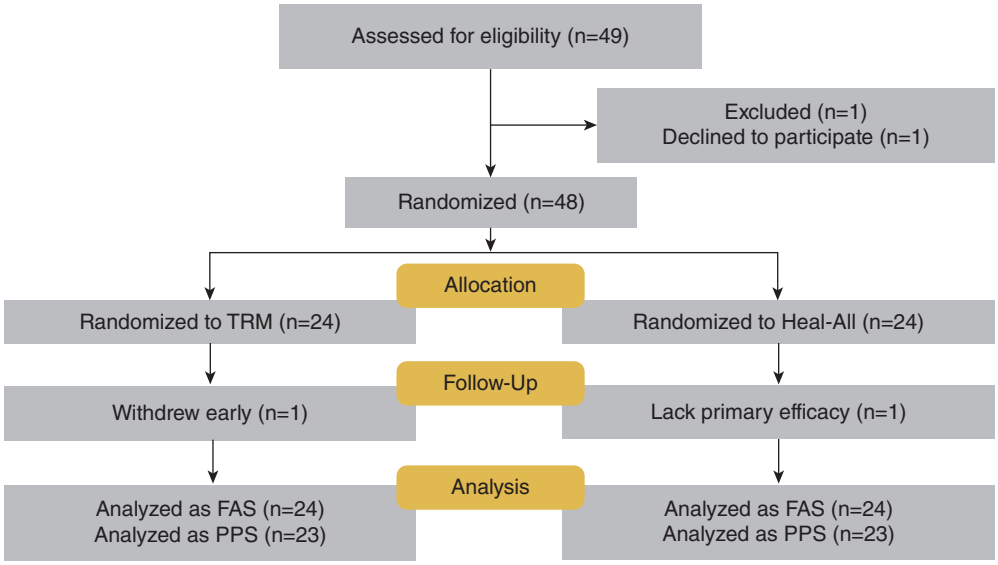

Figure 2. Flow of participants through trial.

Table 4. Baseline characteristics of participants

Demographic Characteristics	TRM Group	Heal-All Membrane Group	*P*
Median age, years	54 (43.00, 58.75)	54 (42.25, 59.00)	.508
Gender (Male/ Female)	13 (54.17%)/ 11 (45.83%)	7 (29.17%)/ 17 (70.84%)	.079
Nation (Han/ non-Han)	22 (91.67%)/ 2 (8.33%)	23 (95.83%)/ 1 (4.17%)	.999
Height/ (cm)	162.46 ±7.08	158.46 ±7.03	.056
Weight/ (kg)	63.83 ±9.32	58.50 ±10.40	.068
Diabetes	6 (25.00%)	3 (12.50%)	.461
Hypertension	11 (45.83%)	12 (50.00%)	.773
Smoking	10 (41.67%)	5 (20.83%)	.119
Allergies	2 (8.33%)	1 (4.17%)	.999
Locations			.043
hard palate	13 (54.17%)	4 (16.67%)	
tongue	4 (16.67%)	10 (41.67%)	
gingiva	4 (16.67%)	7 (29.17%)	
buccal mucosa	3 (12.50%)	3 (12.50%)	
Nature of lesions			.246
carcinoma	7 (29.17%)	2 (8.33%)	
epulis	7 (29.17%)	8 (33.33%)	
fibroma	3 (12.50%)	6 (25.00%)	
papilloma	4 (16.67%)	2 (8.33%)	
oral leukoplakia	1 (4.17%)	2 (8.33%)	
hemangioma	0	3 (12.50%)	
pleomorphic adenoma	1 (4.17%)	1 (4.17%)	
intradermal nevus	1 (4.17%)	0	

Both groups exhibited exceptional performance in incision, suturing, and attachment. The time to achieve Grade A healing was 30.10 ±3.48 days for the TRM group and 30.13 ±3.12 days for the Heal-All membrane group ($P>.05$) using the Student *t* test, with the TRM group taking slightly less time. Surgical area satisfaction was 100% (FAS and PPS) at 10 ±3 days and 1 month ±7 days after surgery for both groups. At 3 months ±7 days after surgery, The TRM group maintained 100% (FAS and PPS), while the Heal-All membrane group was 95.8% (FAS) and 95.6% (PPS).

The normal rate of wound contraction was 100% (FAS and PPS) in the TRM and Heal-All membrane groups at 10 ±3 days after surgery. At 1 month ±7 days after surgery, the TRM group had a normal rate of 100% (FAS and PPS), while the Heal-All membrane group had 91.7% (FAS) and 91.3% (PPS), with the remaining participants showing moderate contractions. By 3 months ±7 days after surgery, the TRM group had a contraction rate of 91.3% (FAS and PPS), while the Heal-All group showed rates of 83.3% (FAS) and 82.6% (PPS). One participant in the Heal-All membrane group with moderate contraction had slightly limited tongue extension, but others with moderate contraction had normal oral function. Typical images are shown in Figure 4. No severe wound contraction was noted in either group.

No significant differences between groups in AEs (7 participants [29.2%] for TRM and 4 [16.7%] for Heal-All membrane, $P=.609$) and SAEs (3 participants [12.5%] for TRM and 1[4.2%] for Heal-All membrane, $P=.303$) using the Fisher exact test. All AEs and SAEs were instrument-independent. No complications occurred. One participant in the TRM group had clinically significant increase in preoperative glucose, and 1 patient in the Heal-All membrane group had a clinically significant increase in preoperative and postoperative glucose, both related to a history of diabetes.

DISCUSSION

The null hypothesis that the lower limit of the 95% confidence interval (CI) of the rate difference between the TRM group and the Heal-All membrane group exceeded −10% was not rejected as the results show no statistically significant differences between groups. The

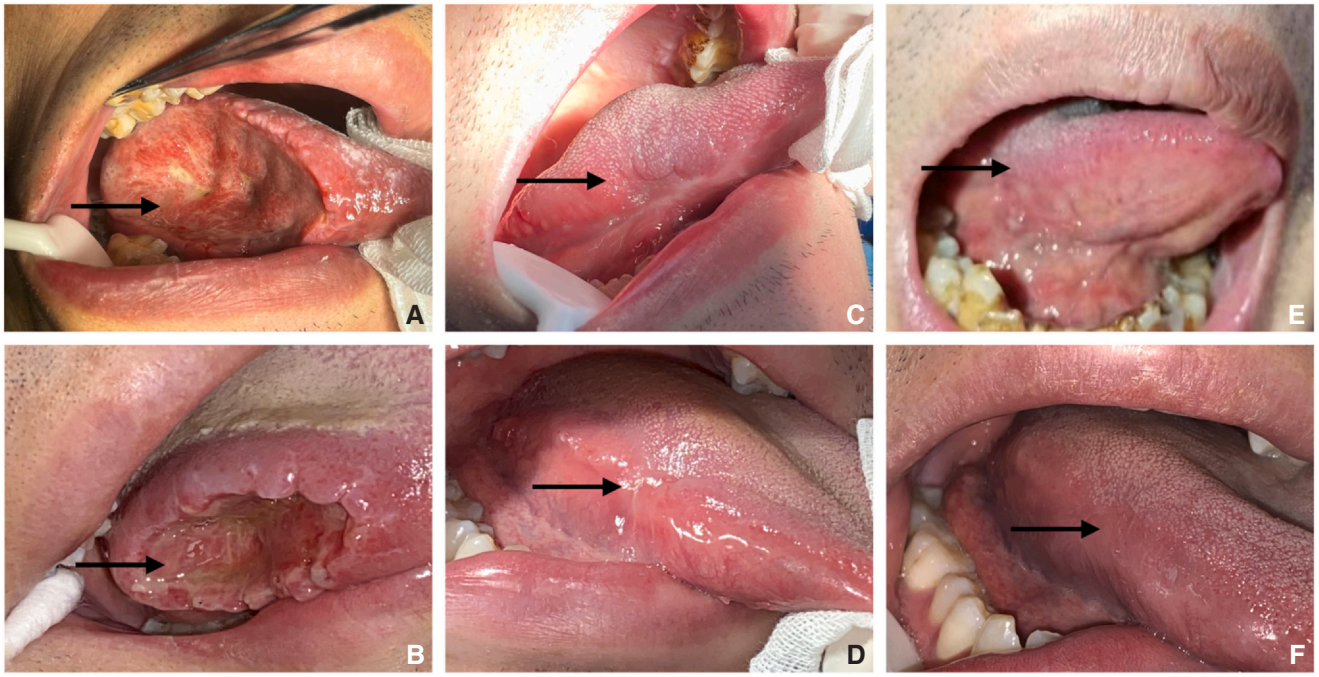

Figure 3. Wound healing after tongue tumor resection. A (trial group), B (control group), Exhibited Grade B healing, without any observable epithelial migration on wound surface at 10 ±3 days after surgery. C (trial group), D (control group), At 1 month ±7 days after surgery, wounds in both groups achieved Grade A healing, indicating excellent healing without any adverse reactions such as redness, exudation, or infection. E (trial group), F (control group), At 3 month ±7 days after surgery, wounds in both groups achieved Grade A healing, indicating excellent healing without any adverse reactions such as redness, exudation, or infection.

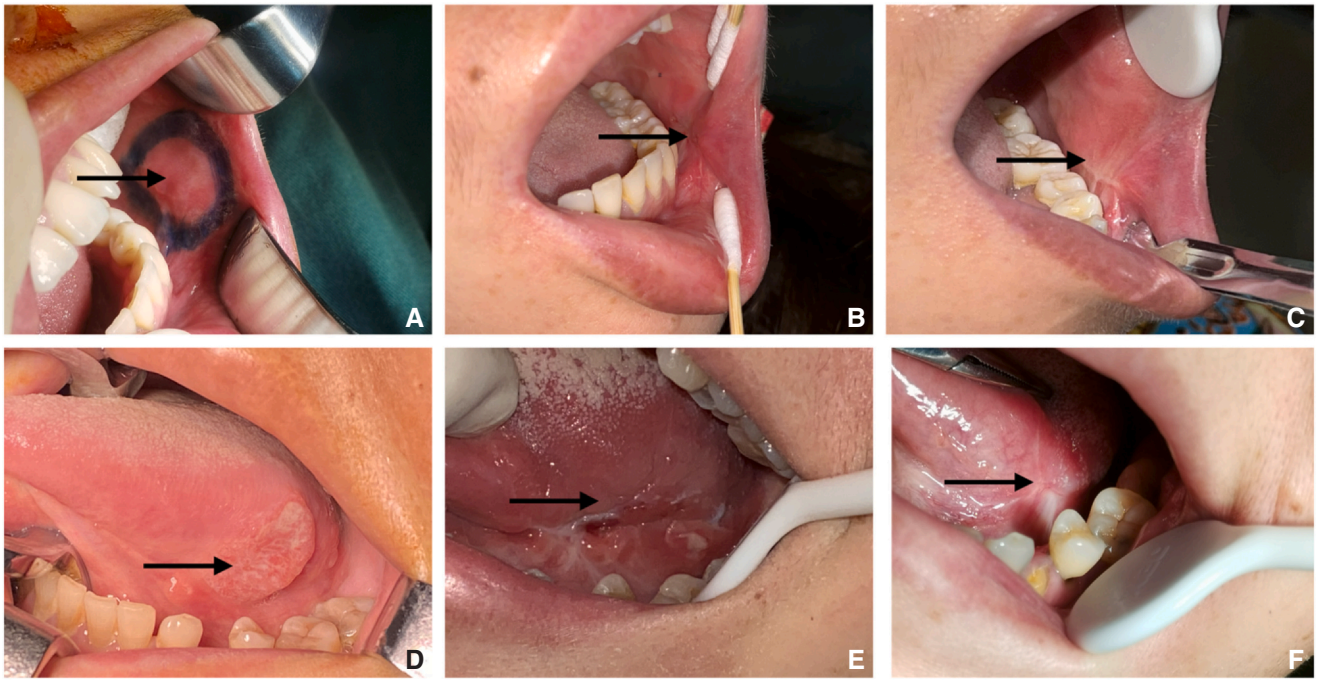

Figure 4. Comparison of wound contraction cases. A, Preoperative images showing buccal lesion in trial group. B, At 1 month ±7 days after surgery, trial group showed moderate wound contraction that was soft and did not impair normal oral function. C, At 3 months ±7 days after surgery, trial group showed moderate wound contraction that was soft and did not impair normal oral function. D, Preoperative images showing tongue lesion in control group. E, At 1 month ±7 days after surgery, control group showed normal epithelial proliferation without wound contraction; F, At 3 months ±7 days after surgery, control group showed moderate wound contraction that was soft, but the contraction resulted in a slight limitation of tongue extension.

electrospinning material TRM and collagen material Heal-All membrane was used to repair oral soft tissue defects in 48 participants, indicating that TRM was as effective as the Heal-All membrane in repairing oral soft tissue defects, regardless of the types of oral diseases, with no significant differences in AEs and SAEs.

TRM displayed excellent intraoperative qualities in this trial, indicating its mechanical stability as a barrier membrane and effectively covered defects, withstanding the complex oral micro-ecological environment. The finding were consistent with those of Mohammad et al,[24] who confirmed the barrier function of Gel/PCL by demonstrating that different cells can grow on both sides without interfering with one another.

As specified previously, the Heal-All membrane used in the control group has limitations. Conversely, TRM in the trial group is a nanoscale structure composed of upper and lower Gel layers and a central PCL layer prepared by using electrospinning technology. Its large SA/V facilitates interactions with cells during tissue regeneration, enhancing cell adhesion and proliferation. Notably, cell adherence to Gel/PCL scaffolds can reach a depth of 114 μm.[25] In addition, the properties of electrospinning materials can be adjusted for defect repair, ensuring the stability and controllability of the healing process.[26] A buccal defect reconstruction experiment in rats by Tango et al[27] revealed that the electrospinning membrane had a tensile strength of 17.7 MPa, significantly higher than that of the Heal-All membrane (7.5 MPa), confirming its better mechanical properties. Wound diameter in the electrospinning membrane group decreased by approximately 74.8% compared with 80.2% in the Heal-All membrane group, suggesting better inhibition of wound contraction. Additionally, the rate of decline in inflammatory cells was faster, and the degradation rate was slower in the electrospinning membrane group. These findings[27] were consistent with those of the present study, suggesting that the electrospinning membrane is more conducive than the Heal-All membrane.

Because of their inadequate mechanical strength, potentially hazardous residual chemicals, thick buildup of fibers, and ethical limitations,[28] most electrospinning-related products have not reached the clinical trial stage.[29] However, studies addressing these shortcomings have been reported, such as modifying the diameter and pore size by adjusting the electrospinning parameters[30] and using the sacrificial layer strategy to selectively remove some of the soluble polymeric elements to enhance cell reaction and distribution uniformity.[31]

Unlike previous research on electrospinning materials, the present research advanced to the clinical trial stage. TRM overcomes traditional electrospinning technology shortcomings while preserving favorable structural qualities. This material ensures biocompatibility, complete biodegradability, and a micro-environment simulating the ECM,[15] consistent with Xu et al,[20] further validating its stability. Based on these research results, TRM, as a novel electrospinning material, appears to have a promising future in the repair of oral soft tissue defects.

Limitations of this study included the demographic restrictions and its single-center nature. Mostly older Chinese participants were recruited, which may limit generalizability. Future multicenter trials with larger sample sizes are needed for improved reliability.

CONCLUSIONS

Based on the findings of this clinical study, the following conclusions were drawn:

1. The efficacy and safety of TRM was noninferior to the Heal-All membrane in repairing oral soft tissue defects.
2. The favorable structural characteristics of TRM suggest potential for further development and improved applications in regenerative medicine.

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CRediT authorship contribution statement
Hong Tang: Project administration, Investigation, Data curation, Writing - review and editing. **Ting Wang**: Formal analysis, Data curation, Writing - original draft. **Pan Zhang**: Software, Validation. **Kai Yang**: Project administration, Funding acquisition, Conceptualization, Methodology, Supervision, Writing - review and editing. H.T. and T.W. contributed equally to this article.

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