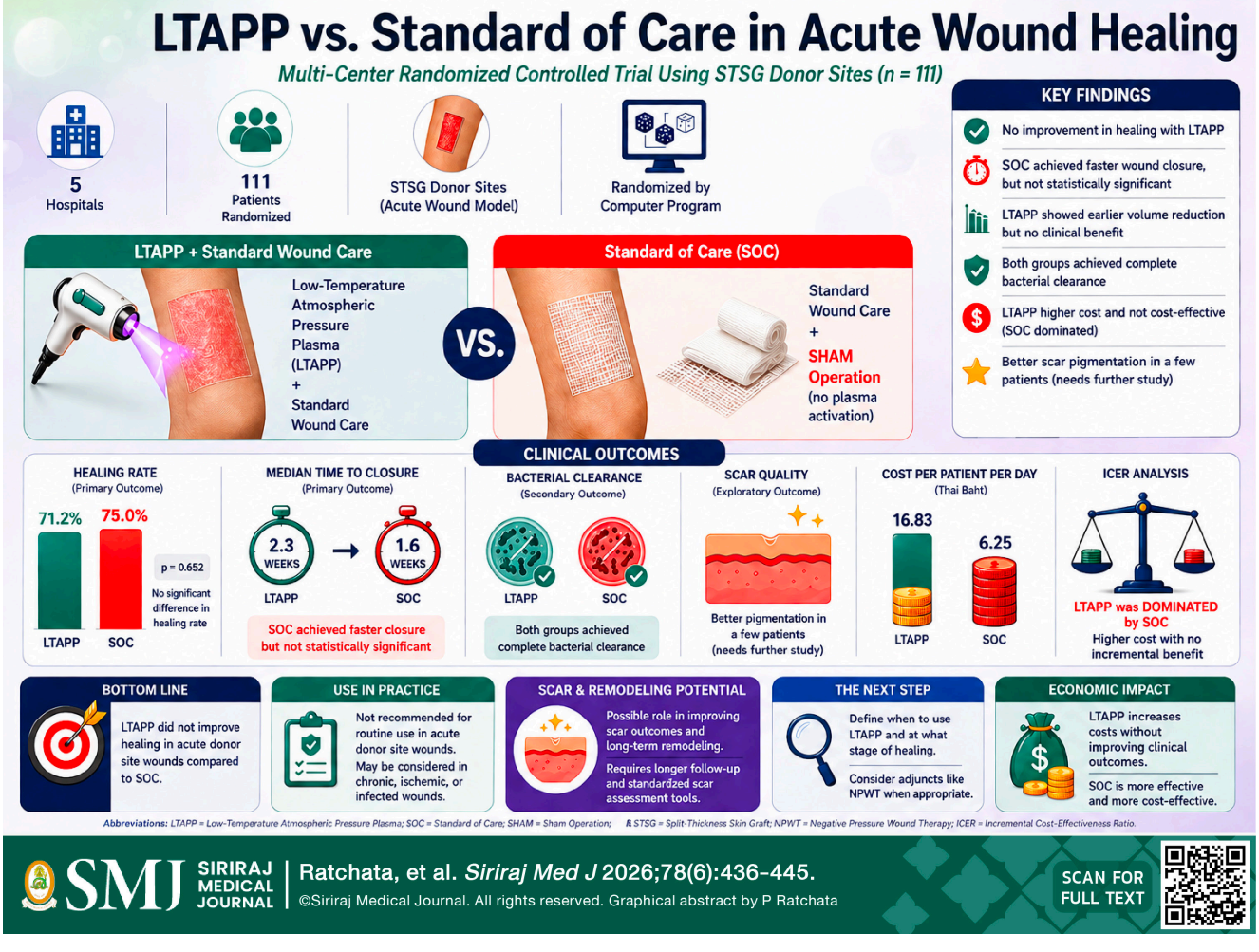
Low-Temperature Atmospheric Pressure Plasma in Acute Wound Healing: A Multi-Center Randomized Controlled Trial Using Split-Thickness Skin Graft Donor Sites as a Standardized Human Model

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ABSTRACT

Objective: To determine whether low-temperature atmospheric-pressure plasma (LTAPP) improves acute wound healing, using split-thickness skin graft (STSG) donor sites as a standardized clinical model.

Materials and Methods: A multi-center randomized controlled trial was conducted across five tertiary hospitals. A total of 111 patients undergoing STSG were randomized to receive standard of care (SOC) with LTAPP or SOC with sham treatment. Primary outcomes included wound healing rates and wound size/volume reduction. Secondary outcomes included exudate clearance, bacterial burden, and cost-effectiveness.

Results: Healing rates were comparable between LTAPP and SOC groups (71.2% vs. 75.0%, p=0.652). SOC achieved faster wound closure (median 1.6 vs. 2.3 weeks), while LTAPP demonstrated earlier wound volume reduction without translating into improved clinical healing. Both groups achieved complete bacterial clearance. LTAPP incurred significantly higher costs and was not cost-effective, with ICER analysis showing dominance by SOC. Better scar pigmentation quality was observed in a few patients.

Conclusion: Using STSG donor sites as a controlled acute wound model, LTAPP did not improve healing outcomes compared to SOC. These findings suggest that LTAPP may have limited utility in uncomplicated acute wounds but reinforce the value of donor site models for evaluating emerging wound technologies. Future research on LTAPP in wounds should focus on chronic, ischemic, or infected wounds where biological modulation may be more impactful.

Keywords: Acute wound model; split-thickness skin graft donor site; plasma medicine; wound healing (Siriraj Med J 2026;78(6):436-445)

INTRODUCTION

Evaluating new wound treatments in clinical practice is often difficult because wounds vary widely in type, patient factors, and local conditions. For this reason, having a consistent and reproducible human wound model is important when comparing different therapies.

Split-thickness skin graft (STSG) donor sites are commonly used as a model of acute wound healing. These wounds are relatively uniform in depth, well vascularized, and tend to heal in a predictable way through re-epithelialization, making them suitable for controlled evaluation of wound treatments.[1,2] Even so, donor site wounds can still be associated with pain, exudate, and occasional delay in healing.

A range of dressing materials has been introduced to improve donor site care. Hydro-fiber dressings containing ionic silver, for example, have been shown to support faster epithelialization and reduce pain compared with conventional paraffin gauze.[2,3] However, no single dressing consistently addresses all aspects of optimal wound healing.

Low-temperature atmospheric-pressure plasma (LTAPP) has gained interest as a potential adjunct in wound care. Plasma generates reactive oxygen and nitrogen species, which have antimicrobial effects and can influence several processes involved in wound healing.[4,5] Nitric oxide produced during plasma application is also known to affect microcirculation, inflammation, and keratinocyte activity.[6] (Fig 1)

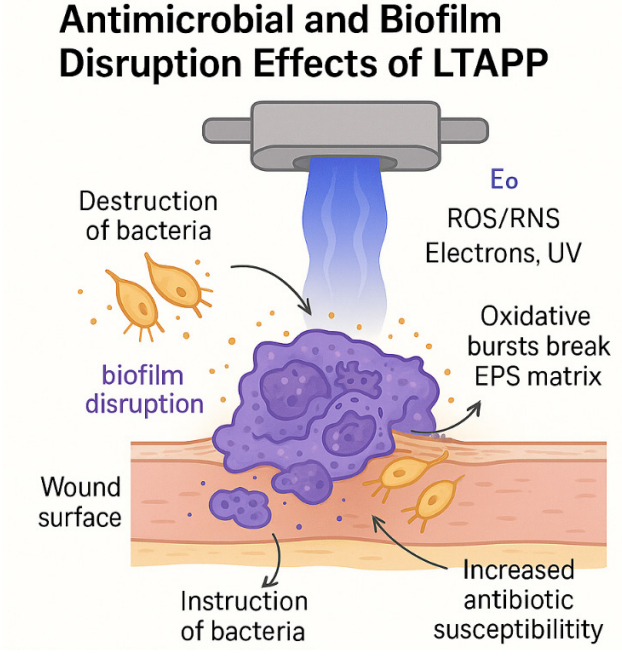


Fig 1. Mechanism of LTAPP on bacteria in wound.

Clinical studies have reported beneficial effects of LTAPP in chronic wounds, including pressure ulcers, where impaired perfusion and bacterial burden contribute to delayed healing. In these settings, LTAPP has been associated with improved wound scores, reduced exudate, and lower bacterial load in randomized studies.[7] Experimental

work also suggests that LTAPP can promote angiogenesis and support tissue repair.[8]

However, it remains unclear whether these benefits extend to acute wounds, where the healing process is usually efficient. A previous randomized study in donor site wounds suggested improved epithelialization with LTAPP, but the evidence is still limited.[1] This study was therefore designed to evaluate the role of LTAPP in acute wound healing using STSG donor sites as a standardized clinical model.

MATERIALS AND METHODS

A prospective, multi-center randomized controlled trial was conducted across five tertiary hospitals in Thailand between September 2021 and May 2023.

Study model: acute wound standardization

STSG donor sites were selected as a **controlled human acute wound model**, providing:

- Consistent wound depth (epidermis and partial dermis)
- Minimal baseline contamination
- Predictable epithelialization

This design minimizes confounding factors commonly present in chronic wound studies.

Participants

Patients aged 18–80 years undergoing STSG were enrolled. Exclusion criteria included:

- Immunocompromised status
- Sepsis or active infection
- Coagulopathy
- Pregnancy
- Concurrent radiotherapy

Randomization and interventions

Participants were randomized by computer-generated number into:

- **LTAPP group:** SOC + LTAPP
- **Control group:** SOC + sham treatment

SOC included saline cleansing, debridement, and standard dressing.

LTAPP was applied every other day for 2 weeks using standardized parameters:

- Frequency: 50 Hz
- Intensity: Level 5
- Distance: 1–3 mm
- Exposure: 1 min/cm^2

Outcomes

Primary outcomes:

- Wound healing rate
- Wound size and volume reduction

Secondary outcomes:

- Exudate reduction
- Bacterial clearance
- Cost-effectiveness (ICER)

Approval for the study protocol was granted by the Central Research Ethics Committee (COA-CREC068/2021).

Statistical analysis

Data were analyzed using SPSS V.25 statistical significance was set at $p<0.05$. Time-to-event outcomes, including time to complete wound healing and time to

TABLE 1. Protocol for interventions.

Visit	1	2	3	4	5	6	7
Day	0	2	4	6	8	10	12
Wound care			Wound care as protocol				
LTAPP			Day 0, 2, 4, 6, 8, 10, 12				
Wound base culture*	✓	✓	✓	✓	✓	✓	✓
Wound assessment	✓	✓	✓	✓	✓	✓	✓
Wound photo collection	✓	✓	✓	✓	✓	✓	✓

wound size or volume reduction, were analyzed using Kaplan–Meier survival analysis and compared using the log-rank test. Hazard ratios (HR) with 95% confidence intervals (CI) were calculated to estimate the relative likelihood of healing between groups.

Median times are presented for descriptive purposes; however, statistical comparisons were based on survival analysis methods rather than direct comparison of medians. Accordingly, p-values for these outcomes reflect log-rank test results.

RESULTS

Baseline characteristics

A total of 111 donor site wounds were analyzed (LTAPP 59, SOC 52). Baseline characteristics were comparable between groups.

Acute wound healing outcomes

Using this standardized acute wound model:

- Healing rates were similar (71.2% vs. 75.0%, p=0.652)
- SOC achieved faster epithelialization
- LTAPP showed earlier volume reduction, but without a clinical advantage

Kaplan–Meier analysis demonstrated no statistically significant difference in time to wound closure between groups. (Fig 2)

Microbiological findings

Both groups achieved complete bacterial clearance, reflecting:

- Low baseline contamination of the model
- Limited added antimicrobial value of LTAPP in acute wounds

Cost-effectiveness

LTAPP significantly increased treatment costs without improving outcomes.

ICER analysis demonstrated **dominance of SOC**.

Safety

No device-related adverse events were observed.

TABLE 2. Demographic data of donor site wounds.

	LTAPP group (n, %) N = 59	SOC group (n, %) N = 52	p-value
Sex			0.091
Male	47 (79.7)	34 (65.4)	
Female	12 (20.3)	18 (34.6)	
Age (mean ± SD)	55.3 ± 15.8	56.0 ± 17.6	0.827
Body mass index	23.9 ± 4.8	26.7 ±18.9	0.295
Comorbidity			
Hypertension	26 (44.1)	27 (51.9)	0.408
Diabetes	23 (39.0)	20 (38.5)	0.955
Dyslipidemia	15 (25.4)	16 (30.8)	0.531
Chronic kidney disease	6 (10.2)	6 (11.5)	0.817
Cerebrovascular disease	2 (3.4)	5 (9.6)	0.249
Location of the thigh			0.613
Anterior	30 (53.6)	24 (49.0)	
Lateral	10 (17.9)	13 (26.5)	
Medial	15 (26.8)	10 (20.4)	
Posterior	1 (1.8)	2 (4.1)	

TABLE 3. The treatment outcomes of patients receiving a combination of LTAPP and SOC treatment compared to those receiving SOC treatment alone.

	LTAPP group (n, %) N = 59	SOC group (n, %) N = 52	p-value
Wound healing			
Number of healed wounds	42 (71.2)	39 (75.0)	0.652
Median time to heal (week; 95%CI)	2.3 (2.0 – 3.1)	1.6 (1.3 – 2.6)	N/A
Wound size reduction[a]			
Number of reduced wound size	40 (67.8)	38 (73.1)	0.544
Number of reduced wound size within 10 days	36 (61.0)	36 (69.2)	0.366
Median time to wound size reduction (week; 95%CI)	1.0 (1.0 – 1.3)	1.0 (1.0 - 1.0)	N/A
Wound volume reduction[b]			
Number of reduced wound volume	51 (86.4)	42 (80.8)	0.419
Number of reduced wound volume within 10 days	50 (84.8)	39 (75.0)	0.199
Median time to wound volume reduction (week; 95%CI)	0.57 (0.43 – 0.71)	1.00 (0.57 – 2.85)	N/A
Wound healing indicators			
Wound exudate reduction	30 (54.5)	34 (68.0)	0.158

Time-to-event outcomes were analyzed using Kaplan–Meier survival analysis; p-values were derived from log-rank tests. Median values are presented descriptively and are not directly compared.
[a]Referred to time after enrollment to achieve 10% reduction of wound area (weeks).
[b]Referred to time after enrollment to achieve 10% reduction of wound volume (weeks).

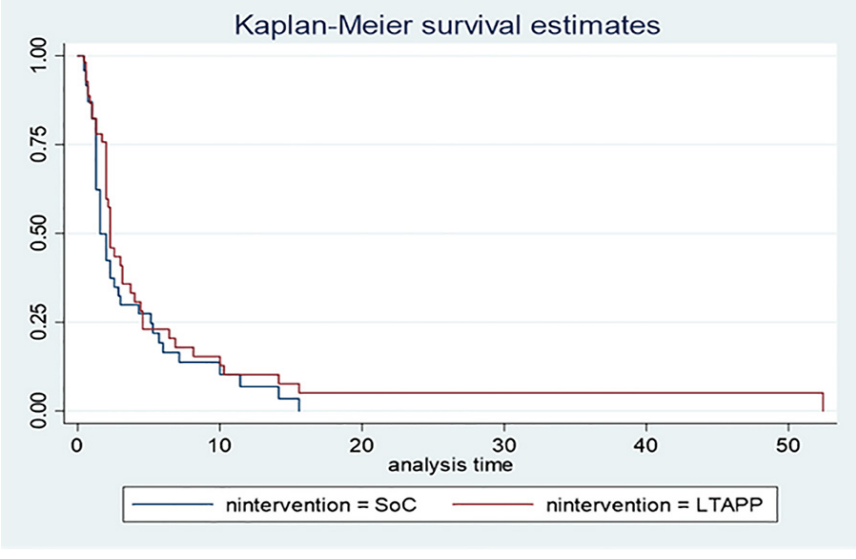


Fig 2. Kaplan-Meier analysis for healed wound in patients with donor site wound.

TABLE 4. The table showed average time of follow-up care of patients in each wound and the cost of materials used and plasma time spent per wound in each visit comparing between LTAPP group and SOC group.

	LTAPP group (median [IQR])	SOC group (median [IQR])	p-value
Average follow-up day (days)	15 [6, 19]	12 [10, 20]	0.318
Total cost (baht/patient)	202 [94, 377.4]	84.5 [56.5 – 550]	0.007
Cost per day (baht/patient/day)	16.83 [14.0, 19.6]	6.25 [5.15 – 17.0]	<0.001

TABLE 5. An incremental cost-effectiveness ratio (ICER) analysis of donor site ulcer between LTAPP group and SOC group

	% of Outcome of LTAPP	% of Outcome of SOC	ICER (Baht/patient/day) (LTAPP vs. SOC)
Size reduction	61.0	69.2	Dominated
Exudate reduction	54.5	68.0	Dominated
Granulation	NA	NA	N/A
Necrotic tissue reduction	NA	NA	N/A
Healed wound	71.2	75.0	Dominated

Note: Dominated indicates higher cost but worse outcome.
Dominant indicates lower cost but better outcome.
ICER means incremental cost for one outcome gained.
Judgmental means lower cost but worse outcome.

DISCUSSION

LTAPP has demonstrated its effect in killing pathogens and chronic wound healing improvement.[1-3] Heinlin J. et al. 2013 found that LTAPP improved healing in split-thickness skin graft donor site.[9] In this study, low-temperature atmospheric-pressure plasma (LTAPP) did not improve healing in split-thickness skin graft (STSG) donor site wounds when compared to SOC (Fig 3). This is not necessarily a negative finding. As a randomized controlled trial, it gives us a clear answer that LTAPP does not add benefit in this type of acute wound.

The model we used is important. STSG donor sites are a good representation of acute wounds. They are uniform, well vascularized, and usually heal in a predictable way.[1-2] In other words, the system is already working efficiently. There may simply not be much room left for an additional therapy to make a difference.

This observation reflects a "ceiling effect" of the acute wound model, in which the baseline healing process is already optimized, thereby limiting the potential for adjunctive therapies to demonstrate additional benefit.

STSG donor sites represent a well-vascularized, low-contamination, and biologically efficient environment, where epithelialization and tissue repair proceed with minimal physiological constraints. In this context, key mechanisms targeted by LTAPP such as antimicrobial

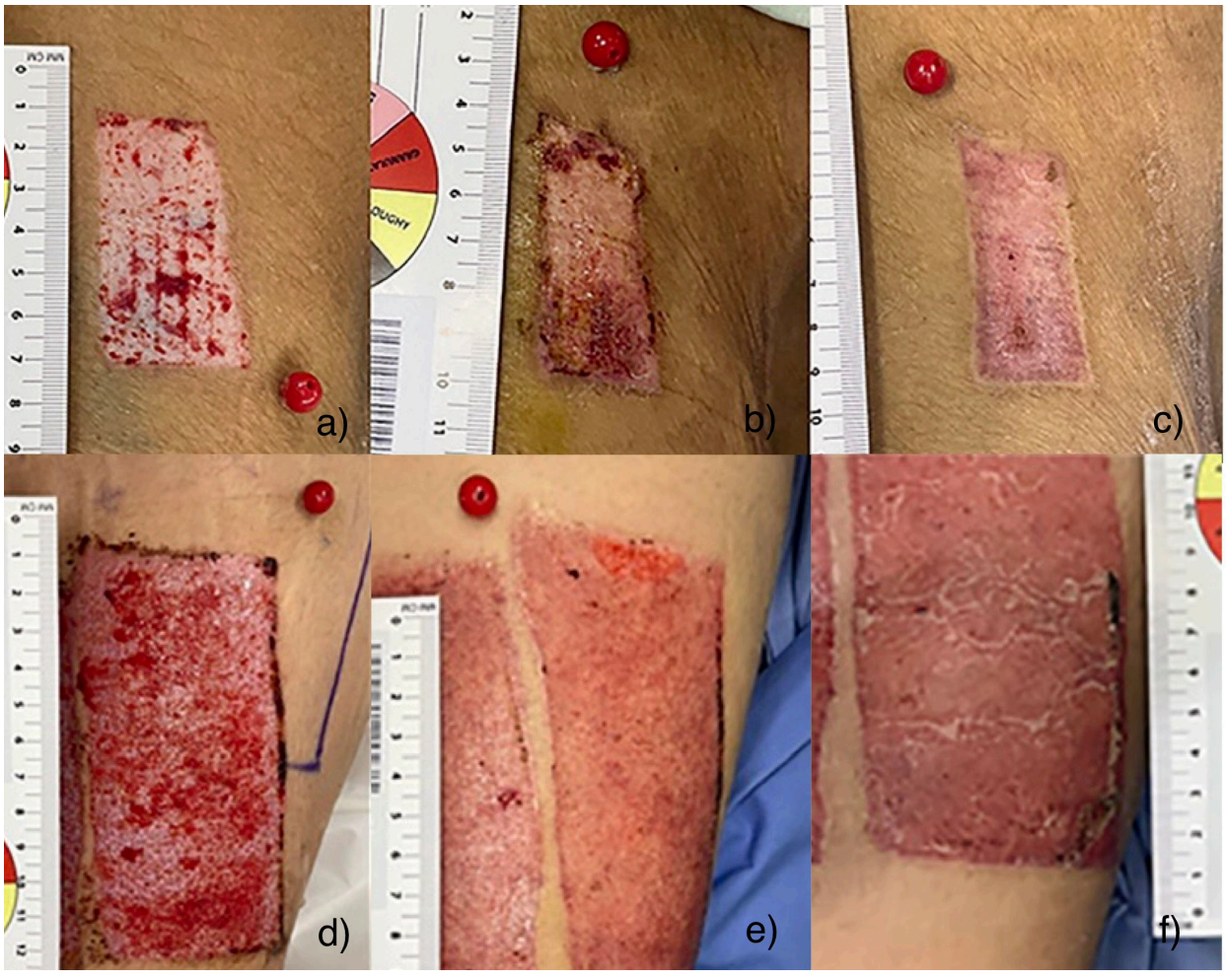


Fig 3. shows the sequence of patient wounds in both groups with the LTAPP group at 1st visit (a), 4th visit (b), and 7th visit (c). The figures show the SOC group at 1st visit (d), 4th visit (e), and 7th visit (f).

activity and enhancement of microcirculation are unlikely to be rate-limiting factors. This concept helps explain the absence of measurable clinical benefit despite the known biological activity of LTAPP. While LTAPP may exert meaningful effects on inflammation, perfusion, and bacterial load, these processes are not the primary barriers to healing in acute donor site wounds.

This likely explains the results. LTAPP targets inflammation, microcirculation, and bacterial burden.[10] In acute wounds, these are not the main problems. Chronic wounds are a different situation. They are often poorly perfused, persistently inflamed, and colonized with bacteria. In that setting, LTAPP is acting on real limitations. Clinical studies in pressure ulcers, for example, have shown better healing and reduced bacterial load with LTAPP.[4] The lack of effect here does not contradict previous studies because it helps define where LTAPP is actually useful.

From a biological standpoint, LTAPP generates reactive species, including nitric oxide, that can influence wound healing.[3] These molecules improve blood flow, support keratinocyte activity, and modulate inflammation. Experimental work also shows effects on angiogenesis and tissue repair.[5] But again, these are not limiting steps in an acute wound that is already healing well.

Another practical point is that current dressings already perform well. Hydrofiber dressings with ionic silver maintain moisture and reduce bacterial contamination compared with standard of care (SOC).[2] With this level of baseline care, it becomes harder for any additional intervention to show a clear benefit.

One interesting finding is the mismatch between early wound changes and final healing. LTAPP reduced wound size early on, but this did not lead to faster epithelialization. This suggests the effect may depend on timing or phase of healing rather than overall speed.

This apparent discrepancy likely reflects phase-specific biological effects of LTAPP. The LTAPP group demonstrated earlier wound volume reduction, yet this did not translate into accelerated epithelialization, indicating that early physical changes in wound characteristics do not necessarily correspond to faster clinical healing.

The generation of reactive oxygen and nitrogen species (RONS), including nitric oxide, may enhance early wound processes such as microcirculation, modulation of inflammation, and granulation tissue formation. These mechanisms may explain the earlier reduction in wound volume observed in this study.

However, re-epithelialization is primarily governed by keratinocyte migration and proliferation, processes that are tightly regulated in acute wounds. In a well-vascularized and biologically optimized model such as STSG donor sites, additional external stimulation may not confer further benefit and may potentially disrupt the balance required for efficient epithelial migration.

Furthermore, a dose-dependent or biphasic effect of LTAPP should be considered. The treatment parameters used in this study (50 Hz, intensity level 5) may influence cellular behavior differently across phases of wound healing. While lower levels of reactive species may promote tissue repair, higher or repeated exposure could alter keratinocyte function without enhancing epithelialization. Although this study was not designed to evaluate dose-response relationships, this hypothesis warrants further investigation.

An important consideration is that the present study primarily evaluated early-phase wound healing outcomes, including epithelialization, exudate reduction, and wound closure within a relatively short follow-up period. These endpoints reflect the inflammatory and proliferative phases of wound healing. However, LTAPP may exert more pronounced effects during the remodeling phase, which was not the outcome in this study. A few reports demonstrated the effect of LTAPP on hypertrophic scar and keloids.[11,12]

In our long-term follow- up in some patients (1-3 years), some individuals in the LTAPP group appeared to demonstrate improved scar quality, including more favorable pigmentation and overall appearance (Figs 4 and 5). However, these observations were exploratory in nature and were not based on predefined or systematically measured outcomes. We acknowledge that scar quality was not included as a primary or secondary endpoint in the original study protocol. Therefore, these findings should be interpreted with caution and considered hypothesis-generating rather than confirmatory.

The absence of standardized scar assessment limits the strength of conclusions regarding the potential effect of LTAPP in the remodeling phase.

Therefore, while LTAPP did not demonstrate superiority in accelerating acute wound closure in this controlled model, it is plausible that it may influence scar quality, including parameters such as hypertrophy, pigmentation, pliability, and overall cosmetic outcome.

This distinction highlights a potential phase-specific therapeutic role of LTAPP—limited in early acute wound healing but potentially beneficial in scar modulation and long-term tissue remodeling. Future studies should incorporate extended follow-up and validated scar assessment tools (e.g., Vancouver Scar Scale or POSAS) to evaluate whether LTAPP can improve long-term outcomes despite neutral effects in the acute healing phase.

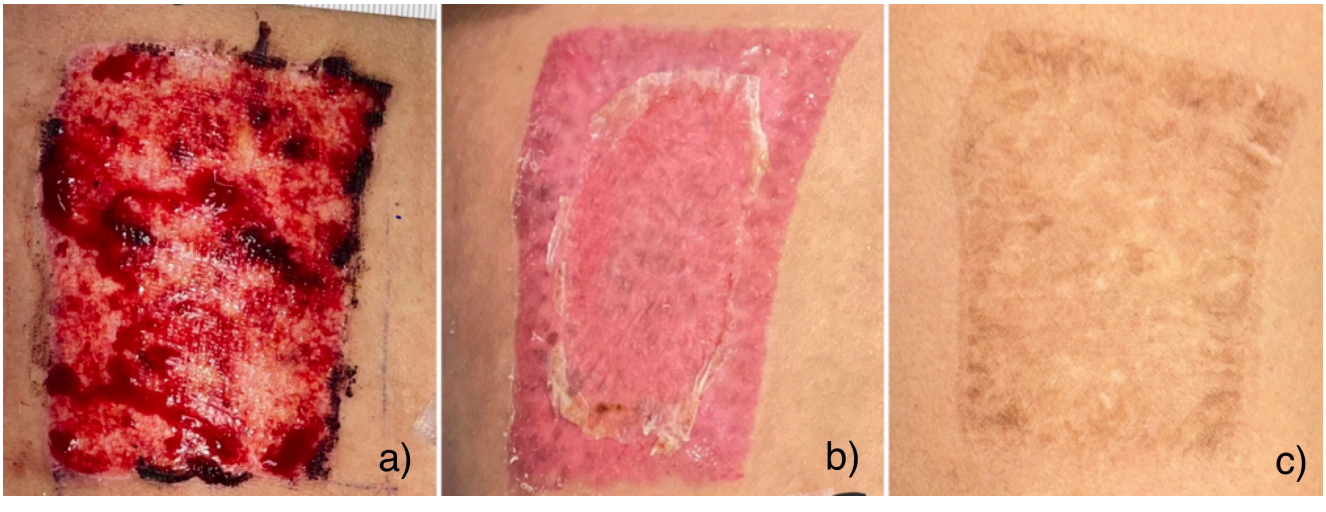


Fig 4. Donor site in the LTAPP group at different time points: (a) postoperative day 3, (b) postoperative week 2, and (c) postoperative year 2.

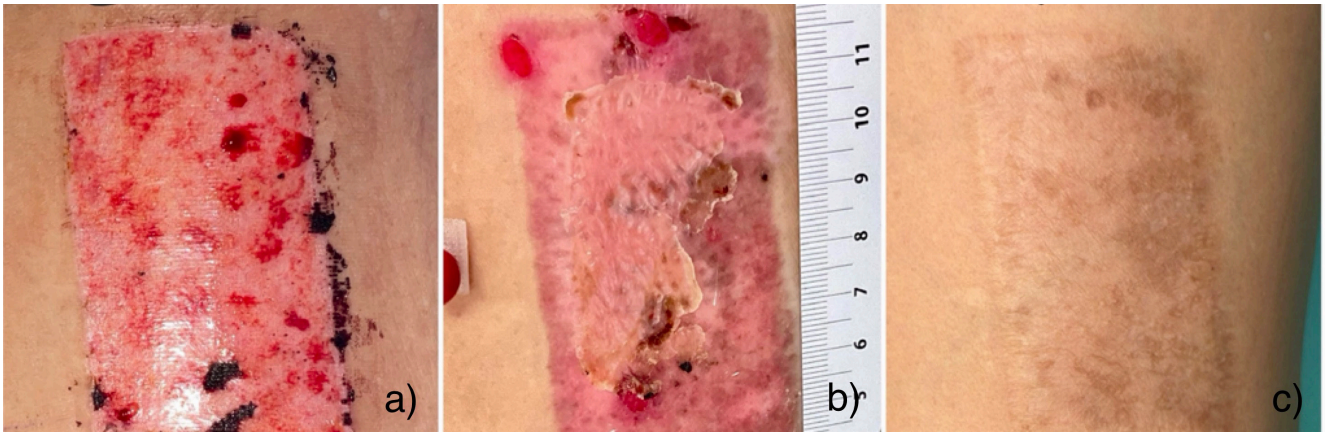


Fig 5. Donor site in the SOC group at different time points: (a) postoperative day 3, (b) postoperative week 2, and (c) postoperative year 2.

In practical terms, LTAPP does not need to be used for routine acute donor site wounds. Its role is likely in chronic wounds, and possibly in improving scar outcomes. The next step is to better define when to use it, and at what stage of healing. In addition, other adjunctive treatment modalities that promote wound healing, such as negative pressure wound therapy (NPWT), may be considered in appropriate clinical settings.[14,15]

As demonstrated, LTAPP significantly increased treatment costs (16.83 vs. 6.25 baht/patient/day, $p<0.001$) without improving clinical outcomes. The ICER analysis consistently showed that LTAPP was dominated by SOC across all evaluated endpoints, indicating higher cost with no incremental clinical benefit.

These findings provide important clinical guidance. In the context of an already efficient acute wound model, the routine use of LTAPP is not justified, particularly in resource-conscious healthcare settings. Rather, these data support a more selective application of LTAPP in wounds where its biological mechanisms target true pathological limitations, such as impaired perfusion, persistent inflammation, or infection.

CONCLUSION

In this multi-center randomized controlled trial, the use of low-temperature atmospheric-pressure plasma (LTAPP) did not improve acute wound healing outcomes at split-thickness skin graft (STSG) donor sites when compared to the standard of care (SOC). Therefore, the routine use of LTAPP for standard donor site care is not currently supported by evidence of clinical or financial benefit. The biological effects of LTAPP, such as antimicrobial activity and microcirculation enhancement, should be redirected toward chronic, ischemic, or infected wounds where these factors are the primary barriers to healing. Although LTAPP did not accelerate the inflammatory or proliferative phases of acute healing, evidence from long-term follow-up suggests a potential phase-specific role in the remodeling phase. Preliminary observations indicated better scar quality, including improved pigmentation and color closer to normal skin, in patients treated with LTAPP.

Data Availability Statement

The data analyzed during the current study are not publicly available due to patient confidentiality and institutional restrictions but are available from the corresponding author on reasonable request.

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DECLARATIONS

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Conflict of Interest

The authors declare no conflicts of interest.

Registration number of clinical trial

The clinical trial was registered with the Central Research Ethics Committee (CREC), Thailand (Registration number: CREC020/64BR-BIO1).

Author Contributions

Conceptualization and methodology, P.R., A.C.; investigation, P.R., P.O., W.T., S.T., N.K., N.P., B.K., C.C.; formal analysis, P.R., O.C., A.M.; data curation, P.O., W.T., S.T., N.P., B.K., K.C., O.C., C.C.; resources, P.O., S.T., B.K., K.C.; validation, P.O., W.T., S.T., N.P., K.C., O.C., A.M., C.C.; visualization, W.T., N.K., O.C., C.C.; supervision, A.C.; project administration, A.C., P.O., K.C.; software, A.M.; funding acquisition, A.C.; writing – original draft, P.R., A.C.; writing – review and editing, P.R., A.C., N.K. All authors have read and agreed to the final version of the manuscript.

Use of Artificial Intelligence

NotebookLM (Google) was used to assist in graphic visualization. All generated materials were carefully reviewed, verified, and edited by the authors to ensure accuracy and alignment with the original study data.

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