

A novel therapy of combination Fractional CO₂ Laser with topical insulin for treating atrophic acne scar: Single arm study

Yuli Kurniawati¹, Sarah Diba¹, Kiki Septiafni¹, Rina Novriani¹, Wenty Septa Aldona¹, Monica Trifitriana²

¹ Department of Dermatology Venereology and Aesthetics, Mohammad Hoesin General Hospital/ Faculty of Medicine Sriwijaya University, Palembang, Indonesia.

² Medical Education Study Program, Faculty of Medicine, Sriwijaya University, Palembang, Indonesia.

Abstract

Introduction Atrophic acne scars pose significant cosmetic and psychological challenges for individuals. Various treatment modalities have been explored, including fractional CO₂ laser therapy and topical insulin, which have shown promising efficacy in scar remodelling and tissue regeneration. The objective of the study is to evaluate the effectiveness and safety of a novel therapy utilizing a combination of fractional CO₂ laser and topical insulin in treating atrophic acne scars.

Methods A total of 19 patients with atrophic acne scars in Palembang were enrolled in this study. The treatment regimen included a combination of fractional CO₂ laser therapy and topical insulin application. Treatment sessions were performed once every two weeks for two months. Scar severity was assessed using validated scales, and patient satisfaction and adverse events were recorded.

Results The combination of fractional CO₂ laser and topical insulin therapy demonstrated promising results in treating atrophic acne scars with significant developments in all outcome variables (Goodman and Baron score, visual analog scale, and quality of life index in dermatology). Significant improvements in scar severity and patient satisfaction scores were observed at the end of the treatment period (at six weeks), with minimal reported adverse events. There is no significant result for random blood sugar with topical insulin influencing blood sugar systemic.

Conclusion A combination of fractional CO₂ laser and topical insulin therapy has been proven effective in treating acne atrophic scars. This treatment option shows promise for managing acne atrophic scars due to its effectiveness and safety.

Key words

Novel therapy; Atrophic scar; Fractional CO₂ laser; Topical insulin; Palembang.

Introduction

Acne vulgaris is a chronic inflammatory disease of the pilosebaceous follicles that can result in permanent acne scars if not treated properly.¹⁻² Acne scars can affect the appearance and quality of life of individuals, as they can lead to decreased academic performance, reduced self-confidence, social isolation, and even depression and suicidal ideation.³⁻⁴ Acne scars are divided

into atrophic, hypertrophic, and keloid scars, with atrophic scars being the most common type.⁵⁻⁶ The treatment of atrophic acne scars

Address for correspondence

Dr. Yuli Kurniawati
Mohammad Hoesin General Hospital/
Faculty of Medicine, Sriwijaya University
Palembang, Indonesia.
Ph: +628127150511
Email: yulikurniawati@unsri.ac.id/
yk_indun@yahoo.co.id

remains a challenge due to varying results, and various therapies can be employed, including topical therapy, systemic therapy, and medical procedures such as chemical peels, microneedling, fillers, subcision, and dermabrasion.⁷

Several studies have shown that fractional CO₂ laser therapy and topical insulin can be an effective options for treating atrophic acne scars. Fractional CO₂ laser therapy has been proven to be more effective than other laser therapies and can serve as laser-assisted drug delivery (LADD) to enhance the penetration of topical drugs such as growth factors found in insulin.⁸ Insulin is a peptide hormone and a growth factor that plays a role in the wound healing process. Topical insulin as a therapy for acne scars has not been extensively researched, but some studies have demonstrated that topical insulin can accelerate the wound healing process without altering blood glucose levels, both in diabetic and non-diabetic patients, with lower costs compared to other topical growth factors and without requiring processes like Platelet Rich Plasma (PRP).⁹⁻¹⁰ The research on the effectiveness of combination therapy with fractional CO₂ laser and insulin for atrophic acne scars is still very limited, which has sparked interest among researchers to conduct further studies.¹⁰

In order to reduce the incidence of acne scars, preventive measures and appropriate treatment for acne vulgaris are necessary. Early and appropriate management is key to reducing the risk of acne scars that can disrupt the quality of life of affected individuals.¹⁰ Therefore, the aim of this study is to determine the effectiveness of combination therapy with fractional CO₂ laser and topical insulin for atrophic acne scars, with the goal of providing an alternative and cost-effective therapeutic option for atrophic acne scars.

Method

This study used an experimental research design with consecutive sampling technique. The minimum sample size for the study was 20 individuals who visited the Dermatovenereology Cosmetic Division Polyclinic of Dr. Mohammad Hoesin General Hospital Palembang during the period of October-December 2022. The sample selection followed the inclusion criteria, which included all patients with atrophic acne scars, mild to moderate degree of atrophic acne scars, and willingness to participate in the study by signing an informed consent form.

The research procedure consisted of several stages. It began with checking the random blood sugar levels 30 minutes before the procedure. This was followed by cleansing the patient's face and applying topical anesthesia for 1 hour before the procedure. Fractional CO₂ laser treatment was performed on the atrophic acne scars on the left and right cheeks, using the following parameters: Fluence 5.1 J/cm², Distance 0.6 mm, and I Stack 3. Afterward, topical insulin [*Saccharomyces cerevisiae* (Actrapid®)] was applied, with a dose of 1 ml on both sides of the face, immediately after the procedure and left to dry for approximately 10 minutes. Cold compresses with 0.9% NaCl were applied to the patient's face for 10-20 minutes. After the procedure, the fasting blood sugar levels were checked 2 hours later. Patients who completed the procedure were required to have follow-up visits every 2 weeks for further therapy. The procedure was performed over 3 sessions (day 0, week 2, and week 4).

The results were analyzed using univariate and bivariate analysis with SPSS version 22.0 (SPSS, Inc., Chicago, Illinois). The results of the Univariate were presented in the form of frequency distribution tables. Furthermore, bivariate analysis was performed to determine

the relationship, mean values, and standard deviations related to the final evaluated outcomes, namely Goodman and Baron score (GBS), Visual Analog Scale (VAS), Dermatology Quality of Life Index (DQLI), and Random Blood Sugar (RBS).

Result

This study is an experimental clinical trial without a control group, conducted from October to December 2022 at the Dermatology, Venereology, and Aesthetics Polyclinic (DKE) of RSMH Palembang. There were 20 research subjects who met the inclusion and exclusion criteria, with 1 patient dropping out due to relocation, resulting in 19 participants who completed the study until the end of the follow-up.

The analysis of characteristics (age, gender, diagnosis) revealed that the average age of the

Table 1 Characteristics patients.

Characteristic	Total (n)	Percent (%)
Age		
15-24 years old	9	47.4
25-34 years old	7	36.8
35-45 years old	3	15.8
Gender		
Male	7	36.8
Female	12	63.2
Diagnosis		
Mild acne scar	10	52.6
Moderate acne scar	9	47.4

patients was 26 years, with a minimum age of 22 and a maximum age of 36. The majority of participants were in the 15-24 age range, comprising 9 individuals (47.4%), while the fewest participants were in the 35-45 age range, with 3 individuals (15.8%). There were more female participants, accounting for 12 individuals (63.2%), and the most common diagnosis was mild acne scars, with 10 individuals (52.6%).

The analysis results (**Table 2**) comparing the

Table 2 Comparison of combination therapy with Fractional CO2 Laser and topical insulin in acne atrophic scars using Visual Analog Scale (VAS), Goodman and Baron score (GBS), and Dermatology Quality of Life Index (DLQI).

Variable	n	Mean (SD)*	Mean change (SD)*	p
Visual Analog Scale (VAS)				
VAS baseline	19	4.42 (0.607)	-	0.000
VAS week 2	19	3.79 (0.787)	0.63 (0.144)	
VAS week 4	19	2.89 (0.809)	1.53 (0.206)	
VAS week 6	19	2.21(0.535)	2.21 (0.507)	
Goodman and Baron score (GBS)				
GBS baseline	19	2.53 (0.513)	-	0.000
GBS week 2	19	2.47 (0.513)	0.06 (0.013)	
GBS week 4	19	1.84 (0.602)	0.69 (0.158)	
GBS week 6	19	1.79 (0.535)	0.74 (0.169)	
Dermatology Quality of Life Index (DLQI).				
IKHD baseline	19	15.58 (6.440)	-	0.000
IKHD week 2	19	15.58 (6.440)	0(0)	
IKHD week 4	19	12.74 (5.626)	2,84 (0.651)	
IKHD week 6	19	10.21 (4.504)	5,37 (1.231)	

*SD: Standard Deviation.

Table 3 Comparison of combination therapy with Fractional CO2 Laser and topical insulin in acne atrophic scars using random blood sugar.

Random Blood Sugar (RBS)	n	Pre Mean (SD)*	Post Mean (SD)*	P value
RBS Baseline	19	91.63 (14.388)	87.63 (9.494)	0,152*
RBS week 2	19	92.79 (9.065)	90.16 (9.155)	0,332*
RBS week 4	19	95.84 (7.669)	88.68 (7.565)	0,000**

*SD: Standard Deviation.

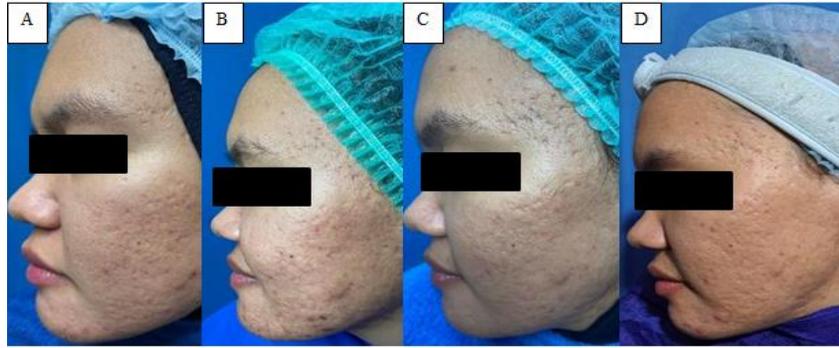


Figure 1 The first patient (A) Baseline (B) After first treatment (C) After second treatment (D) After third treatment.



Figure 2 The second patient (A) Baseline (B) After first treatment (C) After second treatment (D) After third treatment.

combination therapy of fractional CO₂ laser and topical insulin on atrophic acne scars using Visual Analog Scale (VAS), Goodman and Baron Score (GBS), and Dermatology Quality of Life Index (DQLI) with statistical analysis using the Friedman test, revealed significant differences in scores at different time points of therapy (day 0, week 2, 4 and week 6) ($p=0.000$). The mean values showed a decrease in VAS scores from baseline to week 6, indicating that the longer the duration of therapy, the lower the VAS score. The largest mean change was observed at week 6 [2.21 (0.507)], indicating that patients could tolerate pain after several treatment sessions.

Regarding the Goodman and Baron Score (GBS), there was a decrease in the mean values from baseline to week 6, indicating that the longer the duration of therapy, the lower the GBS score. The largest mean change was

observed at week 6 [0.74 (0.169)], suggesting that atrophic acne scars experienced by patients showed improvement after several treatment sessions.

From the assessment of the Dermatology Quality of Life Index (DQLI), there was a decrease in the mean values from baseline to week 6, indicating that the longer the duration of therapy, the lower the DQLI score. The largest mean change was observed at week 6 [5.37 (1.231)], indicating an improvement in DQLI after several treatment sessions.

However, there was no significant difference in the mean RBS values before and after therapy at week 4. The mean values of pre and post RBS from day 0 to week 4 indicated normoglycemic conditions, indicating that the use of topical insulin did not affect the patients' blood sugar levels.

Discussion

Atrophic scars can occur as a result of any inflammatory skin disease that causes significant damage to the epidermal and dermal collagen layers, most commonly seen in acne. Acne scars are classified into atrophic and hypertrophic scars. Atrophic acne scars are further categorized as ice pick, rolling, and box scars.¹¹ This study involved 19 patients with atrophic acne scars who received fractional CO₂ laser therapy with topical insulin.

The characteristics of the patients, including age, gender, and diagnosis, revealed that the average age was 26 years, with a minimum age of 22 years and a maximum age of 36 years. The majority of patients fell within the age group of 15-24 years. These findings are consistent with a study conducted by Arsiwala,² which found a mean age of 24.36±4.37 years in subjects with post-acne atrophic scars who received fractional CO₂ laser therapy combined with topical autologous platelet-rich plasma. The study also showed that there were more female patients (12 individuals), and the most common diagnosis was mild acne scarring, observed in 10 patients. This aligns with the research conducted by Majid,¹² which stated that the majority of patients with acne scars were females with mild acne scars.

The study results also showed that the longer the duration of therapy, the lower the VAS, GBS, and DQLI scores, with the greatest improvement observed in week 6, after three treatment sessions. Based on the observations in this study, it can be concluded that fractional CO₂ laser therapy with topical insulin, as assessed by VAS, GBS, and DQLI, is an effective treatment modality for atrophic acne scars. These findings are consistent with the studies by Sadick¹³ and Lanoue,¹⁴ which stated that the combination of fractional CO₂ laser and topical insulin therapy

shows good effectiveness with tolerable side effects after multiple treatment sessions.

The use of fractional CO₂ laser in the treatment of atrophic scars can enhance the permeability and depth of penetration of topically applied drugs. Fractional laser therapy is a modality that works based on the concept of fractional photothermolysis. The thermal damage caused by fractional laser creates microscopic treatment zones (MTZs) that provide a pathway for drug molecules. Fractional laser therapy creates smaller wound sizes, leading to faster epithelial regeneration compared to non-fractional lasers. Therefore, fractional laser therapy can enhance the penetration of topical drugs into the stratum corneum, epidermis, and dermis.¹⁵

In this study, the topical drug used was insulin. Insulin is a peptide hormone and a growth factor that can promote the healing of damaged skin. Additionally, due to its low cost, the combination of insulin in wound dressings can accelerate healing. Systemic insulin treatment reduces post-surgical infections in diabetic patients and improves pressure ulcer healing. However, this treatment has limitations such as inducing hypoglycemia and hypokalemia. Topical insulin enhances wound healing without altering blood glucose levels in both diabetic and non-diabetic patients.^{16,17}

Topical insulin improves wound healing by regulating oxidative and inflammatory responses. Insulin treatment reduces reactive oxygen species, which can have detrimental effects on lipids, proteins, and DNA. Moreover, topical insulin induces neutrophils and exerts anti-inflammatory effects on wounds by increasing the number of M2 macrophages and IL-10 levels to eliminate dead tissue. Insulin facilitates macrophage chemotaxis, phagocytosis, and inflammatory mediator secretion in vitro by regulating monocyte

chemotactic protein-1 (MCP-1) expression at the wound site.¹⁶

Insulin topical application promotes keratinocyte migration, accelerates re-epithelialization, and enhances fibroblast reactions. Insulin-induced migration and differentiation of keratinocytes depend on the insulin receptor on epidermal growth factor receptor (EGFR), mediated through the PI3K-Akt-Rac1 pathway. Topical insulin treatment for burn wounds increases collagen deposition and formation, as evidenced by increased hydroxyproline levels.¹⁸

In addition to regulating re-epithelialization and the inflammatory response in wound tissue, insulin also exhibits angiogenic effects. Topical insulin increases the formation of newly formed blood vessels in healing tissue. Furthermore, subcutaneous insulin injections stimulate the migration of microvascular endothelial cells and the formation of endothelial tubes. These biological effects are associated with PI3K-Akt-SREBP1 signalling. There is emerging evidence that topical insulin has pro-angiogenic effects and promotes blood vessel formation in diabetic wounds.^{14,16}

The analysis of the comparative therapy with fractional CO₂ laser and topical insulin for atrophic acne scars using Random Blood Glucose (RBG) showed no significant correlation, with pre- and post-treatment values indicating good glycemic control or normoglycemia. This study is consistent with the findings of Wang¹⁷ and Rezvani,¹⁹ which demonstrated that topical insulin does not have a systemic effect on glucose levels. The localized effect of topical insulin is believed to decrease tissue damage caused by glucose metabolism. Therefore, it can be concluded that topical insulin is safe to use and has beneficial effects on wound healing.

Research on the effectiveness of combination therapy with fractional CO₂ laser and topical insulin for atrophic acne scars is still limited. Pawar¹⁰ and Singh²⁰ reported a split-face comparative study comparing combination therapy with microneedling (MN) and Platelet-Rich Plasma (PRP) to MN and topical insulin, and found that both groups showed improvement, but the MN and topical insulin group demonstrated better improvement in atrophic acne scars compared to the MN and PRP group. This is because, after the application of topical insulin, the PI3K/AKT pathway is activated, resulting in increased production of vascular endothelial growth factor (VEGF). Consequently, more type III collagen is produced and matures, and these fibers arrange themselves in a basket-weave pattern, similar to normal skin, as opposed to the transverse pattern seen in scar tissue.^{16,20}

This study is also consistent with a recent review article in 2023 by Amer,²¹ which discusses fractional CO₂ laser and topical insulin, stating that the combination therapy shows good efficacy and can serve as a guideline for the treatment of atrophic acne scars using fractional CO₂ laser and topical insulin.

Limitation This study has limitations, such as a limited sample size, which prevents providing specific conclusions, and the need for a control group to assess more significant results. Further research with a larger sample size and longer observation period is necessary in the field of combination therapy with fractional CO₂ laser and topical insulin.

Conclusion

Combined fractional CO₂ laser therapy and topical insulin have been proven effective for all variable components, including the Goodman and Baron score (GBS), Visual Analog Scale

(VAS), and Dermatology Quality of Life Index (DLQI). The effective therapy duration was observed in week six after three treatment sessions, showing more significant improvements and improved patient comfort. The fractional CO₂ laser and topical insulin did not significantly correlate with Random Blood Glucose (RBG), indicating its safe use without the risk of hypoglycemia. This therapy can be considered a promising option for managing atrophic acne scars due to its effectiveness and safety.

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