

Comparison of the efficacy of carboxytherapy versus fractional CO₂ laser therapy for the treatment of periorbital dark circles: A randomized clinical trial

Hooman Zaheri MD¹ | Amir Mohammad Beyzaee MD² | Ghasem Rahmatpour Rokni MD³ | Anant Patil MD⁴  | Masoud Golpour MD³ | Mohamad Goldust MD^{5,6}

¹Faculty of Medicine, Student Research Committee, Mazandaran University of Medical Sciences, Sari, Iran

²Department of Dermatology, Mazandaran University of Medical Sciences, Sari, Iran

³Department of Dermatology, Faculty of Medicine, Mazandaran University of Medical Sciences, Sari, Iran

⁴Department of Pharmacology, Dr. DY Patil Medical College, Navi Mumbai, India

⁵University Hospital Basel, Basel, Switzerland

⁶University Medical Center Mainz, Mainz, Germany

Correspondence

Mohamad Goldust, University Medical Center Mainz, Mainz 55099, Germany.

Email: drmgjgoldust@gmail.com

Abstract

Background: Periorbital dark circles (PDC) is one of the most common cosmetic issues in today's society. Only moderate degree of improvement has been achieved by various available treatment options. The present study aimed to compare the clinical efficacy of carboxytherapy and fractional CO₂ laser therapy in the management of PDC.

Methods: In this split face study, 30 patients with bilateral PDC aged between 23 and 52 years were recruited who underwent carboxytherapy ($n = 30$) on PDC of one side of the face and fractional CO₂ laser therapy ($n = 30$) on the PDC of other side. The entire treatment comprised of four sessions of each therapy with an interval of 2 weeks each time. The assessment was based on both subjective methods (patients' satisfaction and physician's judgment) and objective method (based on digital standard photographs). The degree of improvement from the patient's point of view (patient satisfaction) and physician's point of view (physician satisfaction) was assessed in different therapy sessions in comparison with the improvement after first session.

Results: The study included 30 patients with mean age of 38.22 ± 8.3 years. The mean disease duration was 45 ± 12.3 months. After the second therapy session, patients' satisfaction was remarkably better in the fractional CO₂ laser therapy group than the carboxytherapy group, over the time. According to the physician satisfaction, the improvement rate was higher after the second and sixth weeks in the fractional CO₂ laser therapy group than the carboxytherapy group; whereas in other sessions, there were no statistically significant differences. There were no significant side effects observed in either group post-treatment each time.

Conclusion: Fractional CO₂ laser therapy is a better option to treat PDC than carboxytherapy. Also, mild side effects (including erythema, pain, and discomfort) were reported in both groups; with no significant difference between the groups.

KEY WORDS

carboxytherapy, fractional CO₂ laser therapy, periorbital dark circles

Patient's global assessment

Visiting / following up times	Therapeutic responses			
	Excellent (75%-100%)	Good (50%-75%)	Fair (25%-50%)	Poor (0%-25%)
Session 1	0	0	17 (56.66%)	13 (43.33%)
Session 2	0	5 (16.66%)	12 (40%)	10 (33.33%)
Session 3	2 (6.66%)	16 (53.33%)	8 (26.66%)	4 (14.33%)
Session 4	3 (10%)	20 (66.66%)	3 (10%)	4 (14.33%)

1 | INTRODUCTION

Periorbital Dark Circles (PDC), bilateral homogenous pigmentation in the periorbital region of the face, are one of the most common issues related to beauty. It can affect a person of any gender and any age group. The pigmentation gets worse with aging.^{1,2}

Generally, PDC is categorized as primary (idiopathic) and secondary, which can be caused by systemic or local factors, including familiar or ethnic tendency, specific anatomic characteristics, post-inflammatory hyperpigmentation secondary to atopic or allergic contact dermatitis, periorbital edema, superficial location of vasculature and shadowing due to skin laxity, tear trough depression, medications, systemic diseases, fatigue, smoking or excessive sun exposure,³ which lead to excessive production of skin pigments in that region.⁴⁻⁶

Numerous treatment options routinely employed to correct PDC are topical whitening medications, chemical peeling, carboxytherapy, laser therapy, injectable fillers, autologous fat transplantation, and blepharoplasty.⁷

The PDC management is very challenging and it's a resistant condition to treat. Fractional CO₂ lasers has been recently used as one of the most effective tools for treating PDC, which breaks the connection of melanosomes of melanocytes, melanophages, and keratinocytes.⁸

There are very limited number of studies to show the efficacy of fractional laser therapy and carboxytherapy.

Hence, we decided to evaluate and compare the efficacy of carboxytherapy and fractional CO₂ laser therapy in the management of PDC.

2 | METHODS

In this study, we recruited 30 patients with bilateral PDC. According to the study of Hassan et al., comparing the efficacy of fractional CO₂ laser against microneedling + TCA 10% in PDC treatment,⁸ the sample size was estimated to 30 subjects.

The exclusion criteria included cases under the age of 18 years, patients who had been treated with topical medication, laser therapy or surgery in the past 6 months for PDC, patients with known history of allergy to fractional CO₂ laser or carboxytherapy techniques, pregnant women and cases receiving immunosuppressive drugs for other dermatoses.

TABLE 1 Patient's global assessment in CO₂ fractional laser for the treatment of PDC

Sub-cutaneous or intradermal injection of pure carbon dioxide at the volume of 5 ml was administered to the PDC of one side of patient's face as carboxytherapy and fractional CO₂ laser therapy was employed to the PDC of other side of the same person. The duration of complete treatment in each of the intervention groups was 6 weeks. Each case underwent four sessions of each treatment at an interval of 2 weeks.

Evaluation of the treatment efficacy was based on both objective and subjective variables. Patient Global Assessment and Physician Global Assessment scales (poor = 0-25%, fair = 25%-50%, good = 50%-75%, Excellent = 75%-100%) were employed. Objective evaluation was based on improving the severity of skin lesions (the darkness of the skin) by viewing serial images taken from the affected areas (Photo-documented). In the initial assessment (screening), before beginning the treatment process, the patients' PDC were photographed by a digital camera (Canon EOS). During the subsequent follow-ups (weeks 2, 4, and 6), the intensity of the pigmentation was compared with the first session. After completing the period of the treatment, the patients were followed up for 1 month. Patients were also evaluated for any complications after treatment.

Treatment Satisfaction Questionnaire for Medication (TSQM) was used as a standard questionnaire to evaluate the side effects, efficacy, and harmlessness of the treatment, and level of patient satisfaction until the end of the treatment process. Dermatology Life Quality Index (DLQI) was recorded in the questionnaire for each patient in order to evaluate patient's quality of life. DLQI was scored from 0 to 30 (no effect = 0-1, minor effect = 2-5, moderate effect = 6-10, large effect = 11-20, extremely large effect = 21-30).

The study was approved by ethic committee of Mazandaran University of Medical Sciences. Written consent was obtained from all the patients.

2.1 | Statistical analysis

Categorical data are presented as numbers and percentages. Mean and standard deviations are provided for the results of continuous variables. Fisher's exact test, Pearson correlation, Chi-Square test, and independent t-tests were used for statistical analysis. Repeated measurement test was used to evaluate changes over time. A *p* value ≤ 0.05 was considered statistically significant. Statistical analyses were conducted using the SPSS software (version 22.0).

3 | RESULTS

The mean age of the patients was 38.22 ± 8.3 years with a minimum age of 23 and a maximum age of 52 years. The mean disease duration was 45 ± 12.3 months with a minimum duration of 6 months and a maximum duration of 20 years. A total of 83.3% of patients were married. The results of patient global assessment and physician global assessment are shown in [Tables 1–4](#).

Patient Global Assessment (PtGA) at the weeks 2, 4, and 6 in the fractional CO₂ laser therapy group and carboxytherapy group had no significant difference ($p > 0.05$) ([Tables 1](#) and [2](#)).

The independent t-test showed that Patient Global Assessment (PtGA) at week 2 and Patient satisfaction (PtS) at weeks 2 and 6 in the fractional CO₂ laser therapy group were significantly better than carboxytherapy ($p < 0.05$; [Table 5](#)). In the repeated measurement test, the time factor was effective in both groups, meaning that during the time the PGA in both groups was significantly reduced. There was an interaction between time and groups, meaning that the decrease in PGA over time in the fractional CO₂ laser therapy group was significantly different from the carboxytherapy group ($p < 0.001$). Also, in relation to Ps, this test showed that Ps in both groups decreased significantly over time, and there was a significant difference between the rate of Ps decrease over time in the two groups and fractional CO₂ laser therapy group decreased more and faster in Ps over time. Fisher's Exact test was used to evaluate the relationship between the two groups and the type of complication, which showed that there was no significant relationship between the two variables ($p > 0.05$; [Table 6](#)). The independent t-test showed that patients' satisfaction with the DLQI and TSQM questionnaires in the fractional CO₂ laser therapy group was significantly higher than the carboxytherapy group ($p < 0.05$; [Table 7](#)).

4 | DISCUSSION

Periorbital dark circles is one of the most common cosmetic issues in today's society and can affect a person of any gender and any age group. In this study, 30 patients with PDC included, they were treated with carboxytherapy on PDC of one side of face whereas PDC of the other side of face was treated with fractional CO₂ laser therapy.

TABLE 2 Patient's global assessment in carboxytherapy for the treatment of PODC

Visiting / following up times	Patient's global assessment			
	Therapeutic responses			
	Excellent (75%-100%)	Good (50%-75%)	Fair (25%-50%)	Poor (0%-25%)
Session 1	0	0	14 (46.66%)	16 (53.33%)
Session 2	0	3 (10%)	16 (53.33%)	11 (36.66%)
Session 3	4 (13.33%)	15 (50%)	6 (20%)	5 (16.66%)
Session 4	5 (16.66%)	18 (60%)	3 (10%)	4 (14.33%)

Carboxytherapy technique improves tissue blood flow, increases skin elasticity and collagen deposition in the skin, reduces fat accumulation and even improves skin lesions after liposuction.^{9,10} Fractional CO₂ laser therapy has recently been used as an effective treatment for PDC, although, some patients discontinue the treatment due to side effects.^{11,12}

As both Co₂ laser and carboxytherapy could have an effect on periorbital edema and skin laxity that exacerbates the appearance of vasculature,¹³ we decided to compare the efficacy and safety of these treatment modalities on PDC.

Our study found fractional CO₂ laser to have superior results compared with carboxytherapy.

A study by Zamanian et al. compared the efficacy of fractional CO₂ laser therapy with a combination therapy of microneedling and 10% trichloroacetic acid (TCA) to eliminate infraorbital dark circles. The above study also found fractional CO₂ laser therapy to have superior results than the 10% microneedling plus TCA. Patients in the laser therapy group were more satisfied with the treatment protocol.⁹ In the present study, the efficacy and satisfaction of patients in the fractional CO₂ laser therapy group was higher than the carboxytherapy group and results were concordant with Zamanian's study. The scales of PGA, PtGA, and PtS were based on the DLQI questionnaire and had similar results in both studies.

Augustyniak et al.¹⁴ had employed non-ablative fractional laser (NAFL) therapy to treat PDC. They reported significantly improve flexibility of the patients periorbital skin. In the present study, the efficacy and satisfaction of patients in the fractional CO₂ laser therapy group was higher than the carboxytherapy group and results were concordant with Augustyniak's study. The scales of PGA, PtGA, and PtS were based on the DLQI questionnaire, and had similar results in both studies.

Bae-Harboe et al. studied the efficacy of fractional CO₂ laser therapy against blepharoplasty to tighten the skin around the eyes and to treat PDC. According to them, fractional CO₂ laser therapy is an effective method with the least side effects against conventional blepharoplasty to treat PDC,¹⁵ similar to our study where fractional CO₂ laser was found to be more efficacious than carboxytherapy.

Manuskiatti et al. studied the role of CO₂ lasers, Q-switched alexandrite lasers, flashlamp-pumped pulsed dye lasers and Er: YAG lasers in the management of melasma and PDC. They found a significant improvement and 75%-100% of patients experienced

Physician's global assessment

Visiting / following up times	Therapeutic responses			
	Excellent (75%-100%)	Good (50%-75%)	Fair (25%-50%)	Poor (0%-25%)
Session 1	0	2 (6.66%)	18 (60%)	10 (33.33%)
Session 2	0	10 (33.33%)	12 (40%)	8 (26.66%)
Session 3	2 (6.66%)	14 (46.66%)	10 (33.33%)	4 (13.33%)
Session 4	9 (30%)	12 (40%)	5 (16.66%)	4 (13.33%)

Physician's global assessment

Visiting / following up times	Therapeutic responses			
	Excellent (75%-100%)	Good (50%-75%)	Fair (25%-50%)	Poor (0%-25%)
Session 1	0	3 (10%)	17 (56.66%)	12 (40%)
Session 2	0	10 (33.33%)	12 (40%)	8 (26.66%)
Session 3	3 (10%)	14 (46.66%)	9 (30%)	4 (13.33%)
Session 4	8 (26.66%)	15 (50%)	4 (13.33%)	3 (10%)

	Carboxytherapy		Fractional CO ₂ laser		
	Mean	Standard deviation	Mean	Standard deviation	p-Value
PtGA-Base	3.80	0.54	3.70	0.65	0.655
PtGA-2	3.68	0.62	2.51	0.85	0.032
PtGA-4	2.85	0.72	2.28	0.71	0.052
PtGA-6	2.50	0.68	2.23	0.46	0.056
P-value	0		0		
PtS-0	3.85	0.90	3.9	0.69	0.45
PtS-2	3.62	0.29	2.34	0.53	0.045
PtS6	2.60	0.57	2.20	0.64	0.05
P-value	0		0		

	Fractional CO ₂ laser		Carboxytherapy		
	Number	Percent	Number	Percent	p-Value
Discomfort	5	16.66%	3	10.00%	0.602
Erythema	3	10.00%	2	6.66%	
Edema	1	3.33%	0	0.00%	
Others	2	6.66%	4	13.33%	

clearing of periorbital hyperpigmented lesions. All the patients responded to the combination therapy of CO₂ lasers with YAG Lasers. Four patients experienced side effects and discontinued the treatment. In their study, the combination therapy of lasers had extraordinary results in the treatment of PDC, telangiectasia, and melasma.¹⁶ In the present study, physician's assessment

correlated with patient's satisfaction. The outcome was superior in the fractional CO₂ laser therapy group than the carboxytherapy group and the results were concordant with the study by Manuskiaiti et al.

To our knowledge, this is the first study to compare effectiveness of fractional CO₂ laser therapy and carboxytherapy for PDC.

TABLE 3 Physician's global assessment in CO₂ fractional laser for the treatment of PODC**TABLE 4** Physician's global assessment in carboxytherapy for the treatment of PODC**TABLE 5** Mean and standard deviation of patient's global assessment and patients' satisfaction scores over time separately**TABLE 6** Number and percent of complications in each group

TABLE 7 Patients' satisfaction based on TSQM and DLQI

	Fractional CO ₂ laser	carboxytherapy	p-Value
DLQI score	13.25 ± 3.52	10.32 ± 3.42	0.002
TSQM score	70.34 ± 10.11	55.23 ± 11.24	0.003

However, studies with a larger sample size and longer follow-up are required to confirm the results of the present study.

5 | CONCLUSION

Though it's a challenge to treat PDC, our study suggests that fractional CO₂ laser therapy is a better treatment option with minor side effects compared with carboxytherapy. Larger studies are required to confirm our observations.

5.1 | Limitation

One-month follow-up is very limited for laser treatment in a disorder like PDC; however, we were unable to follow the patients more, due to lack of cooperation of the patients.

AUTHOR CONTRIBUTIONS

H.Z., A.M.B., and Mo.G. performed the research. Mo.G., G.R.R., and Ma.G. designed the research study. H.Z., A.M.B., and G.R.R. contributed essential reagents or tools. H.Z. and Mo.G. analyzed the data. H.Z. and A.M.B. wrote the paper. A.P. and Mo.G. revised the paper.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICAL APPROVAL

The study was approved by ethic committee of Mazandaran University of Medical Sciences approval number IR.MAZUMS.REC.1399.242.

CONSENT

Written consent was obtained from all the patients.

ACKNOWLEDGMENT

Open Access funding enabled and organized by Projekt DEAL.

ORCID

Anant Patil  <https://orcid.org/0000-0002-9455-4025>

REFERENCES

- Freitag FM, Cestari TF. What causes dark circles under the eyes? *J Cosmet Dermatol*. 2007;6(3):211-215.
- Roh M, Kim TK, Chung KY. Treatment of infraorbital dark circles by autologous fat transplantation: a pilot study. *Br J Dermatol*. 2009;160(5):1022-1025.
- Sarkar R, Das A. Periorbital hyperpigmentation: what lies beneath? *Indian Dermatol Online J*. 2018;9(4):229-230.
- Sardana K, Rajpal M, Garg V, Mishra D. Periorbital hyperpigmentation mimicking fixed drug eruption: a rare presentation of erythema dyschromicum perstans in a paediatric patient. *J Eur Acad Dermatol Venereol*. 2006;20(10):1381-1383.
- Taylor SC. Skin of color: biology, structure, function, and implications for dermatologic disease. *J Am Acad Dermatol*. 2002;46(2):S41-S62.
- Yeh CC, Williams EF. Midface restoration in the management of the lower eyelid. *Facial Plast Surg Clin North Am*. 2010;18(3):365-374.
- Prignano F, Ortonne J-P, Buggiani G, Lotti T. Therapeutical approaches in melasma. *Dermatol Clin*. 2007;25(3):337-342.
- Hassan AM, Hassan GF, Aldalies HY, El Maghraby GM. Treatment of periorbital dark circles: comparative study of chemical peeling with a combination of trichloroacetic acid and lactic acid versus carboxytherapy. *J Surg Dermatol*. 2016;1(2):108-115.
- Zamanian A, Azizi M, Ghazemi M, Behrang E, Naeji S. Comparing the effectiveness of fractional CO₂ laser and the combination therapy with micro-needling and topical 10% trichloroacetic acid to remove infra-orbital dark circles in Tehran women. *J Cosmet Laser Ther*. 2019;21(2):61-64.
- Kontochristopoulos G, Kouris A, Platsidaki E, Markantonis V, Gerodimou M, Antoniou C. Combination of microneedling and 10% trichloroacetic acid peels in the management of infraorbital dark circles. *J Cosmet Laser Ther*. 2016;18(5):289-292.
- Vrcek I, Ozgur O, Nakra T. Infraorbital dark circles: a review of the pathogenesis, evaluation and treatment. *J Cutan Aesthet Surg*. 2016;9(2):65-72.
- Paraskevas LR, Halpern A, Marghoob A. Utility of the Wood's light: five cases from a pigmented lesion clinic. *Br J Dermatol*. 2005;152(5):1039-1044.
- Vavouli C, Katsambas A, Gregoriou S, et al. Chemical peeling with trichloroacetic acid and lactic acid for infraorbital dark circles. *J Cosmet Dermatol*. 2013;12(3):204-209.
- Augustyniak A, Rotsztejn H. Fractional non-ablative laser treatment at 1410 nm wavelength for periorbital wrinkles-reviscometrical and clinical evaluation. *J Cosmet Laser Ther*. 2016;18(5):275-279.
- Bae-Harboe Y-SC, Geronemus RG. Eyelid tightening by CO₂ fractional laser, alternative to blepharoplasty. *Dermatol Surg*. 2014;40:S137-S141.
- Manuskiatti W, Fitzpatrick RE, Goldman MP. Treatment of facial skin using combinations of CO₂, Q-switched alexandrite, flashlamp-pumped pulsed dye, and Er: YAG lasers in the same treatment session. *Dermatol Surg*. 2000;26(2):114-120.

How to cite this article: Zaheri H, Beyzaee AM, Rokni GR, Patil A, Golpour M, Goldust M. Comparison of the efficacy of carboxytherapy versus fractional CO₂ laser therapy for the treatment of periorbital dark circles: A randomized clinical trial. *J Cosmet Dermatol*. 2022;00:1-5. doi: [10.1111/jcd.15337](https://doi.org/10.1111/jcd.15337)