Laser-assisted delivery of vitamin c or vitamin c plus growth factors in the treatment of chloasma in women: a systematic review and meta-analysis

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Abstract

The use of lasers can be an effective approach for treating chloasma in women via the delivery of vitamin C and growth factors. This meta-analysis aimed to assess laser-assisted drug delivery (LADD) vs. traditional techniques for women's skin disorders such as chloasma. According to the "Preferred Reporting Items for Systematic Reviews and Meta-Analysis" (PRISMA) guidelines, we searched the PubMed, ScienceDirect, Google Scholar, Springer, and Wiley online digital libraries. Articles published between 2000 and August 5, 2021, were included in this meta-analysis. A random-effects model was used to determine the pooled risk ratio (RR) with a 95% confidence interval (CI). This meta-analysis included a total of 16 studies. No significant heterogeneity values were observed. A subgroup analysis showed that patients receiving vitamin C plus growth factors had decreased the average wrinkle depth (AD) rates that were more significant than for the patients who received vitamin C alone. Moreover, patients in the treatment group showed greater reductions in the "Melasma Area and Severity Index" (MASI) score than in the control group. This meta-analysis suggested that the laser-assisted delivery of vitamin C plus growth factors should be widely used for certain skin diseases. Future studies need to conduct more trials with large populations using cosmeceutical or other growth factors.

Keywords: laser-assisted delivery; melasma; risk ratio; skin disorders, systematic review

Introduction

Lasers have several applications in the biomedical field, particularly in dermatology. Lasers, as photogenic devices, act as a therapy modality to treat skin disorders. For the last two decades, lasers have shown significant advances in facilitating skin resurfacing and rejuvenation (Lin *et al*., 2014). Fractional lasers promote enhanced drug delivery through the skin. Customized delivery (LADD) has improved the therapeutic consequences for many medical indications. LADD, as an effective technique, increases the dermal uptake of topically used agents. Several studies have been published on LADD techniques, but little is known about their implementation in dermatological practice (Wenande *et al*., 2020).

Melasma, as a common hyperpigmentary disease, affects severely childbearing women. More than 30% of these women are affected by this disease. Melasma has adverse impacts on individual quality of life. An asymptomatic "light to dark brown hyperpigmentation" with irregular borders and symmetrical disposition represents the clinical pattern (Passeron and Picardo, 2018). Melasma is also known as chloasma (e.g., mass of pregnancy). Chloasma has been well defined in the literature as follows: "It is a required hypomelanosis of sun-exposed areas that occurs during pregnancy and can affect 50–70% of pregnant women" (Bolanča *et al*., 2008). Furthermore, the literature states that chloasma typically appears on the cheeks, forehead, and face. Chloasma can occur spontaneously

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but primarily results from taking oral contraceptives or pregnancy (Wang *et al*., 2014).

Although fruits, vegetables, and cereals can be chemically contaminated (Cheng *et al*., 2022; He *et al*., 2021; Hu *et al*., 2021; Ma *et al*., 2022; Rahman *et al*., 2019; Sapkota *et al*.; Sharmin and Ahmed, 2021; Tang *et al*., 2020; Yang *et al*., 2022), they are important sources of vitamins such as vitamin C, vitamin A, vitamin B1, vitamin B2, and vitamin B6 (Ma *et al*., 2021; Sharma *et al*., 2020; Wang *et al*., 2021). Recently, several publications have specified the use of LADD with vitamins to treat skin disorders. Vitamin C or vitamin C plus growth factors GFs was the predominant focus of a small-sample study conducted by Machado *et al*. (Machado *et al*., 2021b). The individuals in the group that was treated with vitamin C and GFs showed significantly reduced skin roughness compared to those treated with vitamin C alone. Moreover, Mann–Whitney tests were conducted to compare the performances of two groups in studies (Machado *et al*., 2021a; Machado *et al*., 2021b). While these studies indicated satisfactory results, the interquartile range (IQR) and median results of the two studies varied. In comparison, another study by Oresajo *et al*. confirmed that vitamin C and ferulic acid protected skin from sunscreen effects (Oresajo *et al*., 2008). As no consensus has been reached among the findings of published studies, the authors of this study conducted a meta-analysis to determine the overall importance of LADD for vitamin C, "cosmeceutical growth factors," and skin disorders.

Material and Methods

Design

This systematic review and meta-analysis were performed according to the updated PRISMA guidelines (Page *et al*., 2021) and recommendations of the Cochrane Collaboration (Higgins, 2011).

Search strategy and selection of studies

The PubMed, ScienceDirect, Springer, Google Scholar, and Wiley online digital libraries were searched for literature that were published between 2000 and August 5, 2021. We also performed a cross-reference search for eligible articles to identify those studies that were missed by a computerized search. A combination of search keywords and MeSH terms was used with the help of Boolean operators described as follows:

> "Laser-Assisted Delivery," OR "Laser-assisted drug delivery," AND "Vitamins," OR "Vitamin C," OR "Growth Factors."

Two colleagues, who are also researchers (e.g., HH and ML), independently assessed the titles and abstracts of the studies using the same inclusion criteria. We resolved any disagreements regarding the inclusion of studies with the consensus of a third researcher (e.g., HL).

Study eligibility and inclusion criteria

The eligibility of the study was evaluated based on the study design approach, participants, comparators, interventions, and outcomes according to the PRISMA guidelines. The participants and interventions were defined as female patients with chloasma disease who received laser treatment with vitamin C. The comparators were defined as those patients who were treated with vitamin C or vitamin C plus GFs for Crohn's disease. There were no restrictions regarding the study design, as both randomized controlled and nonrandomized controlled studies were included in this meta-analysis. The exclusion and inclusion criteria were as follows:

We included studies meeting the following inclusion criteria: (1) all patients who were treated with vitamin C, other vitamins or growth factors; (2) studies mentioning the mandatory use of laser-assisted delivery (LADD) approaches; (3) two study groups, RC (receiving vitamin C) and CGFs (cosmeceutical-containing growth factors) or ROV (receiving other vitamins); and (4) studies published in English.

We did not consider the studies that met the following exclusion criteria: (1) studies on diseases other than melasma or chloasma; (2) seminar reviews, case reports, letters, and reviews; and (3) experiments on animals.

Data extraction

This study involved five researchers. Three researchers (e.g., HH, ML, and HL) independently screened the records that were identified from the database searches. They reviewed the included studies and extracted information at the trial level. The fourth researcher addressed the different opinions among the three researchers regarding data extraction from the studies. Two researchers (e.g., HW and FW) assessed the full-text studies, and another researcher (e.g., HL) repeated this process to provide arbitration with respect to the results. Data extracted from the eligible studies included the study ID (Authors and year), country of the first author, population, LADD model and type, vitamin, growth factors, statistical method, and P-value.

Quality assessment

The Newcastle–Ottawa Scale (NOS) was used to evaluate the quality of the studies included in this meta-analysis(Margulis *et al*., 2014). Two researchers (e.g., HH and ML) examined the quality assessments of the included studies by using the NOS selection, comparability, and exposure categories. Each study was rated based on the three broad perspectives mentioned above. A prospective and cross-sectional study was rated with a maximum of nine stars. A study that received six stars was considered to be of high quality. We resolved any disagreements between the two researchers with the consensus of the third researcher (e.g., HL).

Statistical analysis

We used Review Manager (RevMan) v.5.3.1 to perform the meta-analysis. The Cochran–

Mantel–Haenszel test was used to calculate the pooled estimation (risk ratio) from the categorical variables. The risk ratio (RR) is widely used to determine confidence intervals for unknown populations. The authors determined the RR of individuals receiving vitamin C and vitamin C plus GFs. Similarly, the RR was calculated in this meta-analysis by comparing the LADD and conventional techniques. Forest plots represent the results with 95% confidence intervals (CI 95%).

The I^2 test was used to measure the homogeneity assumption that revealed the percentage of total variation across studies. The level of heterogeneity was considered to be acceptable if the I^2 value was <50% when a fixed-effects model was used. For the random-effects model, the heterogeneity was considered to be elevated when the I^2 value was >50%, and publication bias was visually addressed by using a funnel plot derived from Egger's test.

Results

Study selection

The literature search resulted in the identification of 1095 studies from five popular databases. Of these, 35 records were removed due to duplications, ineligibility, or other reasons. After screening a total of 1060 records, 997 articles were removed as they did not meet the inclusion criteria. Of the 63 potentially articles eligible for the full-text review, we were not able to retrieve 2 papers. A full-text analysis of the remaining 61 studies was performed at the screening stage. Of these studies, 45 were excluded from this meta-analysis. Of these 45 studies, 21 discussed lasers related to other topics, 16 were out of scope, and 8 did not provide the data used in this meta-analysis. Consequently, 16 studies (n = 1095) were selected for use in this meta-analysis (Figure 1).

Study characteristics

Table 1 contains the baseline characteristics of the included studies. As seen in Table 1, two studies were published in each country, which included the UK, USA, Korea, Taiwan, and Philippines. Of the remaining six studies, one was published in each country, which included Japan, Egypt, Turkey, Iran, Brazil, and China. Of the 712 participants who contributed to the included studies, melasma and chloasma were common diseases studied in the included articles. Fractional, CO_2, Q-switched (Nd:YAG), and (Er:YAG) lasers were used to deliver agents in these studies. Three studies did not specify the vitamins used (Ooe *et al*., 2013; Qu *et al*., 2021; Robati and Asadi, 2017). At the same time, vitamin C remained the dominant type of vitamin used in the majority of studies. Two studies mentioned the use of cosmeceuticals (GFs) (Machado *et al*., 2021a; Machado *et al*., 2021b), and one study mentioned basic fibroflast growth factors bFGFs(Waibel *et al*., 2016). A study revealed the growth factors that were released from microneedling procedures. In the included studies, t-tests were predominantly used as the statistical method (Ustuner *et al*., 2017).

Skin disorder control

Three studies with 331 patients (e.g., 136 events in Group A and 254 events in Group B) were used for skin disorder control meta-analysis (Machado *et al*., 2021a; Machado *et al*., 2021b; Rattanawiwatpong *et al*., 2020). Skin roughness (Rgh) or SEr and average wrinkle depth improvements were two necessary outcome measures used in these studies. Baseline skin roughness scores were used to calculate the skin disorder improvements. The patients in the two groups (e.g., A and B) were treated with vitamin C and vitamin C plus GFs, respectively, for different numbers of weeks. We used data on the overall effects on skin roughness to perform the meta-analysis. Figures 2 and 3 show the publication results that were used in this meta-analysis. We took the reduced skin roughness values from the included articles. Three studies using RC and R-CGFs (pooled RR and 95% Cl: 1.50 [1.16–1.96], I^2 = 0.00%) indicated high levels of disorder control by using vitamin C plus GCFs. However, we can measure skin improvements from the perspective of treatment duration, which can further clarify the effects on patients receiving vitamin C plus growth factors.

A total of eight studies qualified for inclusion in the meta-analysis on LADD of vitamin C and vitamin C plus

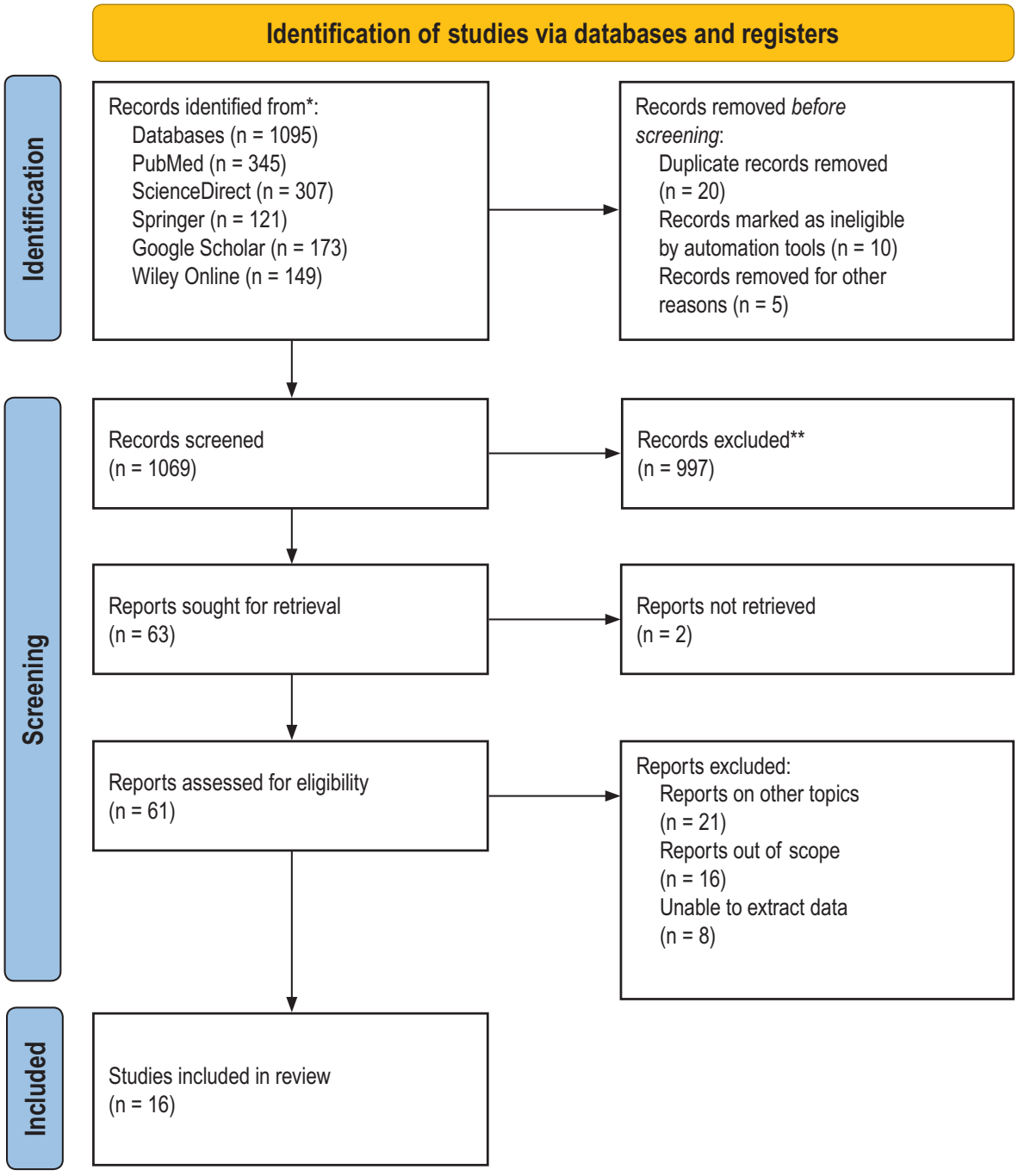

Figure 1. Process selection of papers based on PRISMA.

growth factor GFs. (Alvin *et al.*, 2011; Badawi and Osman, 2018; Choi *et al.*, 2015; Handog *et al.*, 2009; Kim *et al.*, 2020; Lima *et al.*, 2017; Qu *et al.*, 2021; Ustuner *et al.*, 2017). The Melasma area and severity index (MASI) values were used for the control and experimental groups. Pigmentation changes are mainly measured using the MASI scores. Hence, we used the MASI scores at baseline and the end of treatment. Severe hyperpigmentation was associated with higher MASI scores, which reached as high as 48 (Badawi and Osman, 2018). As shown in Figure 3, significant decreases were observed in five studies compared to three studies. The heterogeneity among the included studies was calculated as $I^2 = 0.00$, which indicated no publication bias. The random-effects model was applied to pool data regarding melasma reduction (RR 1.49 95% CI 1.23, 3.65 P = 0.69). Furthermore, we justify our results in this meta-analysis from the recent literature, as shown in Table 1.

Table 1. Study characteristics.

Study ID	Country	Population (characteristics)	LADD model and type	Vitamin	Growth factors	Statistical method
Machado *et al*. (Machado *et al*., 2021b)	UK	N = 132, age (19–62) years, requiring scar treatment	fractional ablative lasers (AFLXs)	C	cosmeceutical	Mann-Whitney test
Machado *et al*. (Machado *et al*., 2021a)	UK	N = 149, age (43–70) years,	fractional ablative lasers (AFLXs)	C	cosmeceutical	Mann-Whitney test
Ooe *et al*. (Ooe *et al*., 2013)	Japan	Age ≥ 20 years and wrinkle score ≥2	YAG laser and other three methods	Not specified	bombined vitamins	t-test, Tukey's test, and Wilcoxon signed-rank sum test
Hsiao *et al*. (Hsiao *et al*., 2016)	Taiwan	N = 8	CO_2 Laser	Two vitamin C	not specified	one-way ANOVA
Choi and Song (Choi *et al*., 2015)	Korea	N = 93 with 440 AK lesions, age >18 years	ablative fractional laser-assisted	not specified	not specified	Pearson's chi-squared test
(Waibel *et al*.(Waibel *et al*., 2016)	USA	N = 15, ages between 30 and 55 years	fractional ablative CO_2 laser	C, E, and Ferulic acid	basic fibroblast (bFGF)	t-test
Kim *et al*. (Kim *et al*., 2020)	Korea	N =18, ages between 26 and 53 years	Q-switched 1064-nm Nd: YAG laser	C, E, and Ferulic acid	not specified	t-test
Badawi & Osman (Badawi and Osman, 2018)	Egypt	N = 30, bilateral melasma	(Er: YAG) laser	C, E, and Ferulic acid	not specified	t-test
Kauvar (Kauvar, 2012)	USA	N = 27 with photo-types (II–V)	Q-switched Nd: YAG laser	C	not specified	Mann–Whitney test and t-test
Ustuner *et al*. (Ustuner *et al*., 2017)	Turkey	N = 16, with recalcitrant dermal	QS-Nd: YAG laser	C	growth factors released by micro-needling procedure	Wilcoxon Signed-Rank
Lee *et al*. (Lee *et al*., 2003)	Taiwan	Not specified	(Er: YAG) laser	C	not specified	t-test
Robati & Asadi (Robati and Asadi, 2017)	Iran	N = 40, ages between 34 and 62 years, and facial rhytides.	ablative fractional lasers (CO_2 and (Er: YAG) lasers	not specified	not specified	Mann–Whitney U and Wilcoxon signed-rank tests
Alvin *et al*. (Alvin *et al*., 2011)	Philippines	N = 50	model not specified	C	mulberry extract oil	Mann–Whitney test
Handog *et al*. (Handog *et al*., 2009)	Philippines	N = 56, melasma	not specified	A, C, and E	oral procyanidin	t-test
Lima *et al*. (Lima *et al*., 2017)	Brazil	N = 6, ages between 34 and 46, melasma	not specified	C	hepatocyte growth factor	t or Wilcoxon test
Qu *et al*. (Qu *et al*., 2021)	China	N = 90, ages between 24 and 49 years, and melasma	fractional CO_2 laser	not specified	tranexamic acid	Kolmogorov-Smirnov and ANOVA tests

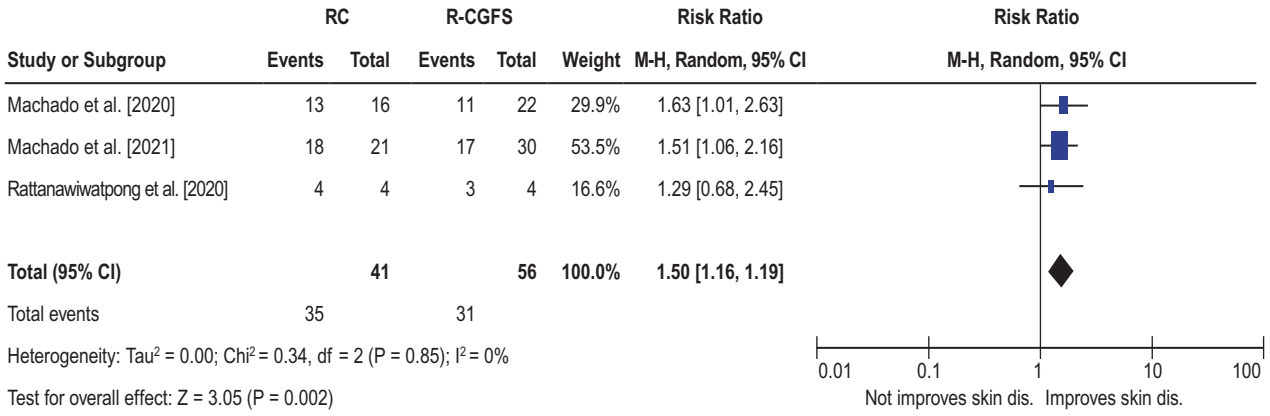

Figure 2. Forest plot of disorder control.

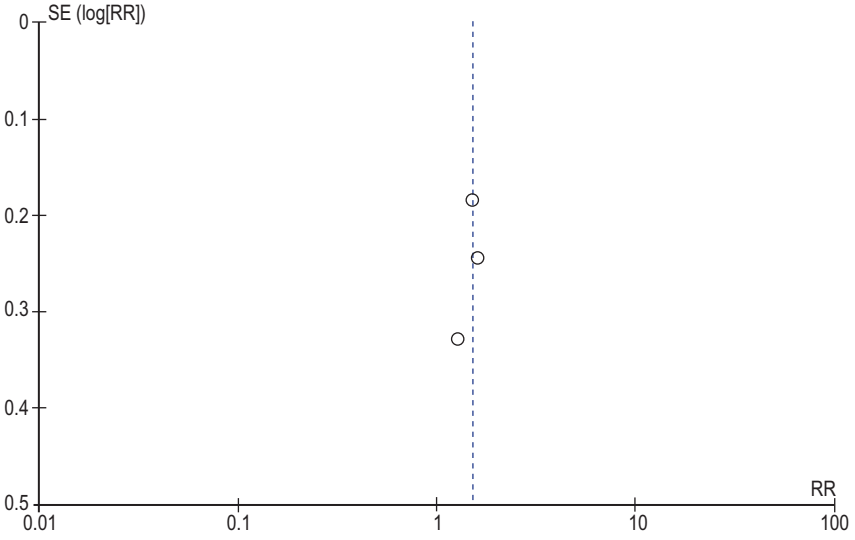

Figure 3. Funnel plot of disorder control.

The data listed in Table 1 indicate that LASER-assisted drug delivery has improved chloasma in women. When the MASI scores of the included studies are compared with the corresponding data from existing studies, it can be verified that the LASER-assisted drug delivery of vitamin C and growth factors decreased the complexities in chloasma.

Heterogeneity test

Two meta-analyses were conducted in this study. The first meta-analysis was performed to assess two study groups, namely, a group that received vitamin C and a group that received vitamin C plus growth factors. In the second meta-analysis, a comparison of two study groups (e.g., control group vs. experimental group) was performed. The heterogeneity I^2 values in the two meta-analyses remained at 0, which suggested no heterogeneity among the included studies.

Publication bias

The diagnostic accuracy of a test is mainly affected by the publication bias in a meta-analysis. A narrower 95% confidence interval was indicative of a high accuracy of a trial. Funnel plots (Figures 4 and 5) were used to evaluate the publication bias (Simmonds, 2015).

Discussion

In this study, two meta-analyses were performed to assess the performance of LADD for vitamin C and vitamin C plus growth factors and to determine how LADD effectively treats melasma or chloasma skin disorders in women.

In the first meta-analysis, three studies qualified for the subgroup analysis of individuals receiving vitamin C and

Study or Subgroup	Control group Events	Total	Experi. group Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Choi et al. [2015]	2	5	1	6	2.0%	2.40 [0.30, 19.34]
Kim et al. [2020]	2	3	2	3	7.0%	1.00 [0.32, 3.10]
Badawi et al. [2007]	3	7	4	9	7.0%	0.96 [0.31, 2.97]
Ustuner et al. [2017]	4	5	3	7	9.6%	1.87 [0.71, 4.88]
Handog et al. [2009]	2	2	2	3	10.7%	1.33 [0.54, 3.32]
Alvin et al. [2011]	5	8	4	6	14.6%	0.94 [0.43, 2.04]
Qu et al. [2021]	9	13	6	13	18.7%	1.50 [0.75, 2.99]
Lima et al. [2017]	29	46	11	37	30.3%	2.12 [1.23, 3.65]
Total (95% CI)		**89**		**84**	**100.0%**	**1.49 [1.11, 2.01]**
Total events	56		33			

Heterogeneity: Tau² = 0.00; Chi² = 4.73, df = 7 (P = 0.69); I² = 0%
Test for overall effect: Z = 2.63 (P = 0.009)

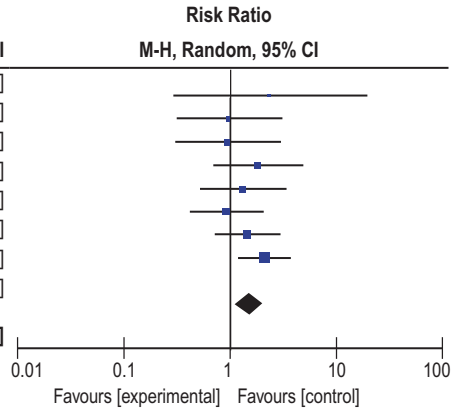

Figure 4. Forest plot of a comparison between two techniques using MASI score.

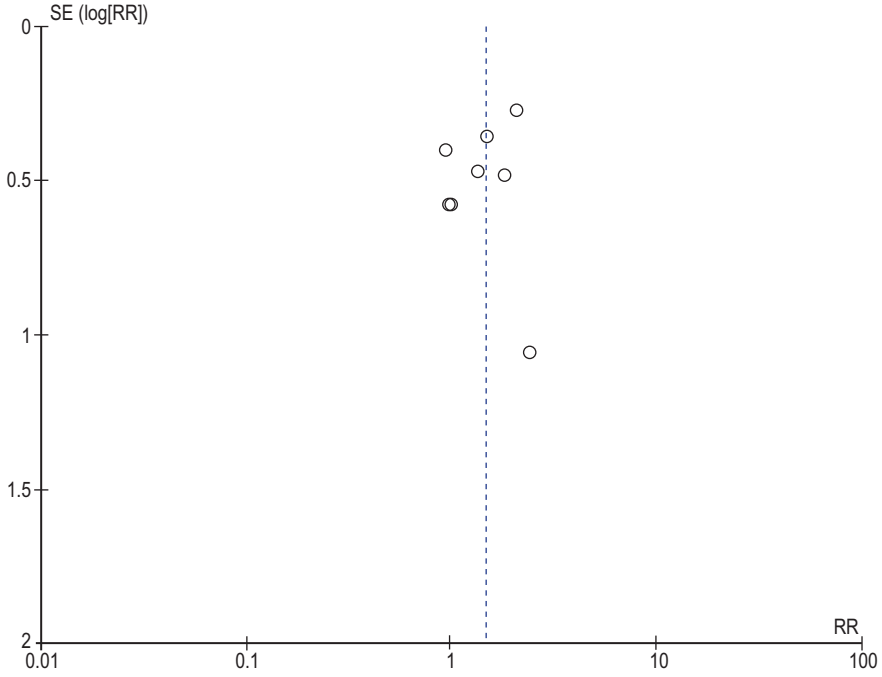

Figure 5. Funnel plot of a comparison between two techniques.

vitamin C plus GFs. For this case, cosmeceutical GFs were used in three studies. This meta-analysis indicated that a combination of vitamin C plus CGFs assisted by LADD yielded better results than vitamin C alone (Figure 2). The subgroup analysis showed decreased skin disorder severities (e.g., melasma or chloasma) in both groups (e.g., A and B), but LADD with vitamin C plus CGFs significantly decreased wrinkles and skin roughness. This was achieved by analyzing the Rgh or SEr values after using vitamin C and C plus GFs. The baseline values, as shown in Figure 2, were different in the three studies.

Second, eight studies qualified for the subgroup analysis of LADD (control vs. experimental groups) used for treating melasma or chloasma disorders (Figure 3). The results of the meta-analysis indicated significant treatment differences in the patients of the two groups. A significant reduction in MASI scores was observed in the experimental group compared to the control. The MASI scores significantly decreased in five studies, while they remained either unchanged or were slightly lower in three studies. These results might be due to variations in treatment periods and the agents used in the studies. For example, one study reported that microneedling sessions

continued for 30 days (Lima *et al*., 2017), while in another study, patients were treated with a combination of antioxidant serum for 2 weeks (Kim *et al*., 2020).

An earlier meta-analysis discussed the microneedling technique when used for topical therapies in melasma disorder (Bailey *et al*., 2021). Furthermore, a study was performed to observe the safety and efficacy of acupuncture for chloasma (Liang *et al*., 2017). This is the first meta-analysis conducted to evaluate LADD for vitamin C and growth factors. Moreover, this meta-analysis first showed that the LADD technique decreased wrinkles in patients of both the two groups.

This meta-analysis has several strengths. Primarily, studies were conducted in different regions that involved different age groups. The I^2 values in both meta-analyses remained at 0.00, which indicated no heterogeneity. There was no publication bias in the present meta-analyses.

Our study has two main limitations. The results of two meta-analyses need to be interpreted with caution. First, the number of studies and individuals in these meta-analyses was relatively small. Second, different types of laser devices were used, and their influence varied over various platforms.

Conclusions

Numerous LADD trials have been conducted to treat certain skin disorders (e.g., melasma or chloasma) with vitamin C and vitamin C plus growth factors. Overall, the LADD technique is more effective than traditional techniques in treating these skin disorders. In summary, this meta-analysis suggests evaluating more growth factors in a large population in future studies.

Conflict of Interests

The authors declare that they have no conflicts of interest.

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