



REVIEW ARTICLES

Systematic review of clinical studies assessing the needling for treatment of melasma: Focusing on efficacy, safety, and recurrence rate

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Abstract

Background and objective: Melasma is common, chronic and treatment-challenging cosmetic concern and the aim of this study was to systematically evaluate clinical studies assessing the treatment of melasma through needling while focusing on efficiency, safety, and recurrence.

Method: After e-search a total of 54 articles were reviewed and 12 published articles (February 2011-September 2020) in terms of content, topic, and purpose, were finalized. Articles were open pilot trials, case reports, case series, retrospective studies, quasi-experimental trials, randomized clinical trials, and split face comparative studies.

Results: The highest decrease in MASI score was 85.71% and allocated to microneedling method following only 3 sessions with an interval of 30 days. On the other hand, the lowest decrease in this score was 3.7% and allocated to microneedling treatment and its use for vitamin C delivery at the end of the fourth week of treatment. No side effects were reported in included studies, and the various needling methods used were safe. Recurrence after treatment was reported in none of these articles, and only one of them reported a 4% recurrence in the second phase of treatment, but no recurrence was reported in the last phase of that study.

Conclusion: Non-aggressive microneedling with topical depigmenting agents was more effective than topical depigmenting agents alone, so that the mean MASI score was significantly higher than those who used lightening serum alone. So needling can be suggested as an effective and safe method with low recurrence rate for the treatment of melasma.

KEYWORDS

dark skin, hyperpigmentation, melasma, microneedling, systematic review

1 | INTRODUCTION

Melasma is a common and prevalent pigmentary *cosmetic* disorder of the skin, in which symmetrical brown macules irregularly develop on sun-exposed areas of the body, especially on the face, and it is

more common in women and dark-skinned individuals.^{1,2} Numerous factors are involved in the incidence of melasma, such as genetic influences, sun exposure, pregnancy, oral contraceptive pills, estrogen-progesterone therapy, thyroid disorder, Serum iron level, cosmetics, and medication.³⁻⁵ The prevalence of melasma varies

from 1.5% to 33.3% depending on the population,⁶ and its prevalence is higher in people of Asian, Latin American, and Spanish descent as well as individuals with Fitzpatrick skin types IV.⁷ For these patients, melasma is a real disturbing problem that may have a significant impact on their quality of life. According to dermatologists, the treatment of this disease is the biggest concern.⁷ Common treatments for melasma include eliminating potential causes with the use of sunscreen and depigmenting agents, such as hydroquinone, kojic acid, azelaic acid, *oxy arbutin*, ascorbic acid alone or in combination, such as Kligman's formula.⁸⁻¹⁰ Hydroquinone has been used as the gold standard treatment for melasma, since 1950. Kligman's formula including hydroquinone with retinoic acid and dexamethasone has been the most effective treatment for melasma since 1975, but it is associated with skin atrophy due to the presence of corticosteroids in its formula, which is used as a therapeutic agent.¹¹ Excessive use of this treatment method has also highlighted the side effects of this triple formula.¹² These treatments do not necessarily cure the cause of melasma, and their effectiveness will vary in patients. Even after treatment, the skin discoloration may not always be completely disappeared, and the patient may have to try different treatment options to achieve the desired result. In addition, some therapies may be performed consistently to maintain treatment results.¹³ Recently, treatments such as laser therapy have found a special place in the treatment of melasma.¹⁴ Though cost-effective, treatments requiring daily and long-term use are extremely tiring for patients, often do not lead to a full recovery, and have no lasting effect after discontinuation. Therefore, treatments such as laser therapy, mesotherapy, and skin needling have recently been considered. In order to achieve better results in the treatment of melasma, the topical use of skin lightening agents in combination with procedures for increasing the drugs' skin penetration, such as electroporation, sonophoresis, and iontophoresis, has been suggested in the last few years. Recently, skin needling has been described as a new technique that can improve the absorption of transdermal drug.¹³ Types of skin needling include microneedling, mesoneedling, and radiofrequency microneedling. Through successive piercing of the skin with sterilized microneedles, microwounds are created in the skin during microneedling treatment, and then, growth factors are secreted, triggering collagen production.¹⁵ In addition, microneedling-induced epidermal thickness increases protection against UV. Microneedling can also lead to the delivery of topical medications.¹⁶ Fabbrocini et al. investigated the combined effect of microneedling and depigmenting serum as a means to enhance the transdermal penetration in the treatment of melasma as a means to enhance the transdermal penetration of a serum. Their results showed that patients treated with combined microneedling and depigmenting serum had a statistically significant decrease in their MASJ scores and luminosity index, and their clinical symptoms improved significantly compared to patients treated with depigmenting serum alone.¹³ In another study, microneedling therapy was evaluated in 18 women and 4 men with recalcitrant melasma. All patients experienced good outcomes in the aforementioned study. The researchers concluded that microneedling could be a promising treatment for melasma.¹⁷ The purpose

of this systematic review was to evaluate the original articles studied different types of needling therapies, including microneedling, mesoneedling, and radiofrequency, for the treatment of melasma, and to extract their data to explore the effectiveness, side effects, and durability of treatment. Since melasma treatment is challenging and there is no gold standard treatment with the same effect on all patients, in this study, we tried to evaluate the effectiveness, side effects and reliability of the needling as new emerging method for treatment of melasma.

2 | MATERIAL AND METHOD

The present study evaluated the effectiveness, side effects, and reliability of needling therapy in the treatment of melasma from 2000 to 2020. For this purpose, the databases of PubMed / MEDLINE, Embase, PsycINFO, TRIP Cochrane, and Cochrane Skin were searched. This systematic clinical review included open pilot trials, case reports, case series, retrospective studies, quasi-experimental trials, randomized clinical trials, and split face comparative studies. Inclusion criteria were including at least one needling treatment group and reporting the results of needling effectiveness. Studies not written in English or addressing needling as a treatment for melasma were excluded. Data from review studies and non-original articles were not included, either. The keywords of needling, melasma, microneedling, mesoneedling, and radiofrequency were used during search.

The Cochrane Risk of Bias scale was used to assess the quality of articles (according to this protocol, articles were divided into three categories based on the bias line: low, high, and indistinguishable).

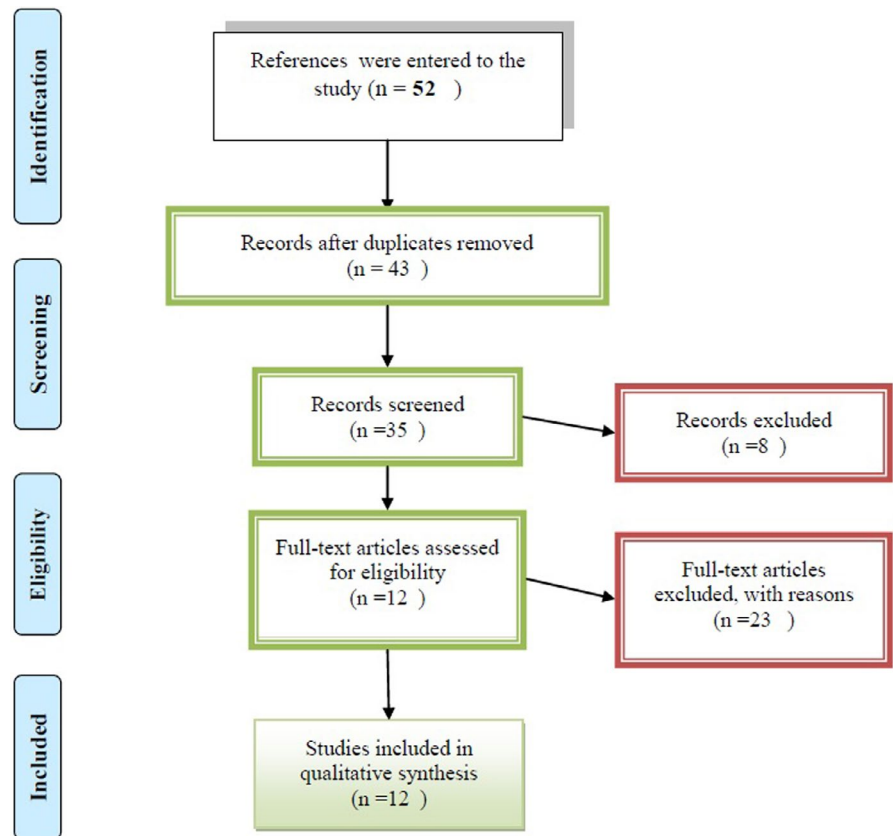
The articles were evaluated in terms of various methodological aspects, including sampling methods, reliability of the tools used, and the objectives. Finally, articles that were appropriate in terms of subject coverage and content structure were used in this study. The e-search was conducted on a total of 52 articles and 12 ones, which were published from February 2011 to September 2020 and were related in terms of content, topic, and purpose, were finalized.

Figure 1 shows the PRISMA chart of the study.

3 | RESULTS

In the present study, a total of 12 original articles were reviewed. The included articles were open pilot trials, case reports, case series, retrospective studies, quasi-experimental trials, randomized clinical trials, and split face comparative studies (Table 1). In the reviewed articles, a total of 377 patients were treated, of whom 340 were female and 17 were male. The mean age of the patients was 39.34 years old. The types of melasma reported in these articles were melasma on both sides of the face, facial refractory melasma, recalcitrant melasma, localized melasma, and bilaterally symmetrical melasma. There were 17 patients with Fitzpatrick skin type 2, 48 patients with type 3, 69 patients with type 4, and 22 patients

FIGURE 1 PRISMA chart of the study



with type 5. The average number of treatment sessions was 4. The maximum number of sessions was 10 and the minimum number of sessions was 2. These treatment sessions were performed with an average interval of 22.44 days. The maximum time interval between sessions was 30 days, and the minimum was 7 days. Microneedling was applied in 83.33%, mesoneedling in 33.8%, and radiofrequency in 25% of the reviewed articles. In 66.66% of the articles, the needling method was compared with another method. These methods included ND: YUG lysis, fractional carbon dioxide laser, depigmenting serum, tranexamic acid, and vitamin C. In addition, in 25% of all articles studied, needling method was used for delivery of various drugs, such as tranexamic acid, MD: melanoceuticals (from kojic acid, tranexamic acid, azelogyline, arbutin, glycolic acid, ascorbic acid, citric acid, glutathione), and vitamin C. Among the reviewed articles, only one article (8.33%) used the severity index (PSI) score for evaluating the results and scoring. In other articles (91.67%); however, the Melasma Area Severity Index (MASI) was used to evaluate the effect of treatment. Based on the extracted data, the highest decrease in MASI score, which means improvement in the treatment of melasma, was 85.71% and allocated to microneedling method following only 3 sessions with an interval of 30 days. On the other hand, the lowest decrease in this score was 3.7% and allocated to microneedling treatment and its use for vitamin C delivery at the end of the fourth week of treatment. Based on these results, the average decrease in MASI score was 3.72. No side effects were reported in included studies, and the various needling methods used were safe. Recurrence after treatment was not reported in none of these articles.

The quality of articles submitted for review was assessed by the Cochran scale. The results of quality evaluation of articles are presented in Table 2. According to the Cochran evaluation scale, only one study in 5 areas of bias had a risk of bias, three studies in three areas had a risk of bias, and two studies had a risk of bias in two areas. Other studies had unclear levels of bias risk in the four areas of selection bias, performance, reporting, and types of bias.

4 | DISCUSSION

Although melasma is a pigmentation disorder that is difficult to treat, new treatments have been developed. These techniques, namely skin needling electroporation, sonophoresis, and iontophoresis, are capable of transdermal drug delivery and increase the absorption of local agents through the skin.¹⁸ The use of skin needling has been suggested as a new physical strategy to increase transdermal drug delivery.¹³ This method has been used since 1995 to achieve percutaneous collagen induction to reduce skin imperfections. To date, skin needling has been suggested as an effective method in treating wounds and wrinkles. This technique is done by rolling a special device on the skin consisting of a roller cylinder equipped with a variable number of microneedles.¹³ Microneedling is a minimally invasive procedure that involves sequential piercing of the skin with sterile microneedles, which is used to treat many skin concerns. The resulting microwounds lead to secretion of growth factors and production of collagen, limiting side effects such as the risk of infection and ulcers. Given that the epidermis is relatively healthy in this method,

TABLE 1 Summary of reviewed articles

	Title, year, and type of trial	Number of the participants, type of melasma, and type of needling	Treatment arms and distances	Efficacy, side effects, and reliability of treatment
1	<p>Skin Needling to Enhance Depigmenting Serum Penetration in the Treatment of Melasma</p> <p>Fabbrocini et al (2011)</p> <p>8 authors</p> <p>A pilot study¹³</p>	<p>Participants: 20 female patients with melasma in both sides of their faces, aged between 32 and 60 years old (mean age: 53 years), and suffered from Fitzpatrick skin types III - V.</p> <p>6 patients (30%) type III</p> <p>9 patients (45%) type IV</p> <p>5 patients (25%) type V</p> <p>Method: Rolling a 12 cm plastic handle attached to the cylinder like a small paintbrush on the skin, 20 mm in diameter and 20 mm long.</p> <p>The surface of the cylinder consisted of 24 circular rows of 8 needles (192 needles in total), the length of the needles was 0.5 mm and their diameter was 0.02 mm, resulting in about 250–300 needles per square centimeter</p>	<p>After local anesthesia on the left side of the face, the needle cylinder was rolled over the melasma areas. Depigmenting serum was then applied on the treated areas. Depigmenting serum alone was applied on the melasma left hemi-facial areas. This procedure was repeated twice with a one-month interval. In order to achieve better results, at the end of the first treatment, each patient was taught how to use a home roller device and depigmenting serum in the melasma areas of the right side of the face. Patients underwent this treatment every day for two months. The home roller device was applied horizontally, vertically, and diagonally to the right and left 8 times in each direction. Immediately after that, the standard amount of depigmenting serum was applied. The results were analyzed using the Melasma Area Severity Index and Spectrocolorimeter X-Rite 968 for up to two months</p>	<p>The results showed that in areas treated with skin needling in combination with depigmenting serum, hyperpigmentation was significantly reduced compared to treated areas using only depigmenting serum. The mean index L in the group treated with skin needling +depigmenting serum was 64.97 and in the group treated with depigmenting serum alone was 61.61 after treatment. Comparing luminosity index (L) before and after treatment, the improvement (increase in brightness) was 17.4% in patients treated with needling and serum, and was 11.2% in patients treated with serum only. In the right side of the face treated using skin needling therapy +depigmenting serum, the mean baseline score of MASI (19.1) decreased to 14.4 one month after surgery ($p < 0.001$). In other words, it decreased 22.64%. Two months after surgery, it decreased to 9.2 (41.4%) ($p < 0.001$).</p> <p>In the left side of the face treated with depigmenting serum alone, the mean baseline score of MASI decreased from 20.4 to 17.4 ($p < 0.05$) (14.71%) one month after surgery and to 13.3% (34.81%) two months after surgery</p> <p>No side effects were reported</p>

TABLE 1 (Continued)

	Title, year, and type of trial	Number of the participants, type of melasma, and type of needling	Treatment arms and distances	Efficacy, side effects, and reliability of treatment
2	<p>Combined Use of Monopolar Radiofrequency and Transdermal Drug Delivery in the Treatment of Melasma</p> <p>Cameli et al (2014)</p> <p>4 authors</p> <p>Case report¹⁸</p>	<p>Participants: 50 women with melasma between the ages of 30 and 60 and suffering from Fitzpatrick skin type II to IV.</p> <p>4 patients (8%) type II</p> <p>24 patients (48%) type III</p> <p>22 patients (44%) type IV</p> <p>Method: Combined monopolar radiofrequency with medium frequency electrical pulse (480 kHz) and transdermal drug delivery (hydroelectrophoresis) at low frequency current (10 Hz) with output compatible with skin impedance was used</p>	<p>Patients underwent 6 sessions of treatment at one-week intervals. During each session, 5 ml of Phyto complex gel containing 1% kojic acid was applied immediately before the start of complete facial treatment. Phyto complex gel was delivered through a quick-release skin delivery system consisting of a generator - RF energy pulse emitter (480 kHz) and low frequency modular current (10 Hz) connected to a steel handle with an electrode inside (diameter: 25 mm, thickness: 3 mm) and a neutral return plate. No topical depigmenting treatment was used in patients recommended to use daily sunscreen (SPF 50). Each patient underwent a clinical skin examination before treatment (T0), 1 month (T1), and 6 months (T2) after the end of treatment using Melasma Area and Severity Index (mMASI) and Melasma Area and Severity Index (MASI) to assess the severity melasma</p>	<p>The results showed that hyperpigmentation decreased significantly 1 month after the last treatment session (T1) and at 6-month follow-up visit (T2) compared to T0. The mean MASI score decreased from 21.3 to 15.7 (26.3%) (One month after the end of treatment $p < 0.001$) and reached to 16.9 (20.66%) in 6-month follow-up measurements. No side effects, such as erythema, ulceration, and post-inflammatory hyperpigmentation, were observed or reported at 1-month and 6-month follow-up visits. It was concluded that the combined use of unipolar RF with transdermal depigmenting drugs can be a safe and effective non-invasive treatment for melasma. The recurrence rate of melasma was 0% in T1 and 4% in T2</p>

(Continues)

TABLE 1 (Continued)

	Title, year, and type of trial	Number of the participants, type of melasma, and type of needling	Treatment arms and distances	Efficacy, side effects, and reliability of treatment
3	Microneedling in facial recalcitrant melasma: report of a series of 22 cases Lima (2015) 1 author Case series ¹⁷	Participants: 22 patients (18 females and 4 males) who aged 22 to 40 years old and two patients aged >40 years old were recruited. Patients suffered from recalcitrant melasma. Method: A tool with 1.5 mm long needles was used	Local anesthesia was applied with 4% lidocaine cream 30 minutes before. The treatment was continued with back and forth movements approximately 10 times in 4 directions by pulling four overlapping bands, resulting in diffuse redness of the skin and intermittent bleeding. After 24 h and in the following days, patients were instructed to use industrial depigmentation formula (0.05% tretinoin +4% hydroquinone +1% fluocinolone acetone) and industrial sunscreen with SPF 60 at night. The same procedure was performed 30 days after the first treatment	One hundred percent of the patients were satisfied with the treatment outcomes. The amount of pain during treatment was well tolerated by 16 patients (70%) and 6 patients (30%) reported that they did not feel any pain. Eleven evaluated patients are under 24-month follow-up after the first procedure and their skin brightness remains unchanged.
4	Assessment of the effects of skin microneedling as adjuvant therapy for facial melasma: a pilot study Lima et al (2017) 4 authors An open pilot trial ¹⁹	Participants: 6 women with facial refractory melasma who aged between 34 and 46 old. Patients had Fitzpatrick type III and IV. Method: Microneedling with a 1.5 mm needle was performed	These patients were treated for two sessions with an interval of 30 days (T0 and T30) and the day after treatment used a daily triple combination and sunscreen (SPF 70). mMASI and MASI were used to assess the severity melasma	After two microneedling sessions, improvement in melasma was observed in all patients, and there was a report of facial smoothness and more luminosity by the patients. There was a 70% decrease in MASI and a 13% increase in luminosity index (L). Patients were treated with sunscreen and triple combination for 6 months. No recurrences were observed

TABLE 1 (Continued)

	Title, year, and type of trial	Number of the participants, type of melasma, and type of needling	Treatment arms and distances	Efficacy, side effects, and reliability of treatment
5	<p>Combined treatment of melasma involving low fluence Q-switched Nd:YAG laser and fractional microneedling radiofrequency</p> <p>Kwon et al (2018)</p> <p>4 authors</p> <p>A retrospective study¹⁴</p>	<p>Participants: 114 patients with melasma were included. Fifty-six patients received combination therapy (mean age 32 years, 53 females and 3 males) and 58 patients received QSNY (mean age 33 years, 56 females and 2 males). Patients had localized / diffuse melasma and Fitzpatrick type III / IV / V.</p> <p>Method: The treatment settings of the FMR device were as follows: 0.5- to 1.0 mm microneedle penetrating depth, 20 to 30 intensity, and 30 to 50 ms duration with 1–2 passes</p>	<p>For 10 sessions at one-week intervals, the combined treatment group was treated with QSNY and FRM consecutively, while the QS toning group was only treated with QSNY. Patients in the QSNY group were treated with homogeneous flat beam profile and fluidity of 3 J / cm² with PTP mode at 10 Hz for 10 sessions at one-week intervals. In the combined treatment group, the FRM device was applied sequentially after QSNY with the same regimen settings. No anesthetic cream was applied to either group. All patients were instructed to use a broad-spectrum SPF 50 during the treatment session. mMASI and MASI were used to assess the severity melasma</p>	<p>The combined therapy had higher efficacy compared to QSNY therapy. Both groups had a moderate degree of reduction in mMASI score (2.9 vs. 1.8). ΔmMASI was 2.9 in the combined group and 1.8 in the QSNY group. The baseline mMASI score was 5.82 in the combined group and 5.98 in the QSNY group. There was a 49.83% decrease of mMASI score in the combined group and a 32.78% decrease in the QSNY group. No significant difference was observed between the two groups in terms of treatment-related side effects, while the prevalence of mottle hypopigmentation and rebound hyperpigmentation was higher in the QSNY group.</p>

(Continues)

TABLE 1 (Continued)

	Title, year, and type of trial	Number of the participants, type of melasma, and type of needling	Treatment arms and distances	Efficacy, side effects, and reliability of treatment
6	<p>Comparative Efficacy of Oral Tranexamic Acid and Trans-epidermal Delivery of Tranexamic Acid by Micro-Needling in Melasma Gupta et al, (2019) 5 authors A prospective randomized study²⁰</p>	<p>Participants: 30 patients (24 females and 6 males) with a mean age of 34.4 years old who suffered from melasma. Group A received tranexamic acid (TxA) by microneedling and Group B received oral tranexamic acid (TxA). There were 15 patients in each group. Patients had Fitzpatrick type III and IV. Method: The microneedles used were a ZGTS derma roller impregnated with 192 fine titanium needles of 1.5 mm length and 0.25 mm diameter. They can penetrate to a depth of 0.1 to 1.3 mm of the skin. Microneedling was performed vertically, horizontally, and diagonally for about four to five times, followed by the use of TxA solution. This procedure was repeated three times in one session</p>	<p>Group A received TxA solution (4 mg / ml) through microneedling every 4 weeks. Group B received 250 mg of oral TxA for twice daily and for 12 weeks. All patients in both groups used the same sunscreen. MASI was used to assess the severity melasma</p>	<p>The decrease in MASI score was greater in the oral TxA group, but there was no statistically significant difference between two groups in this regard (5.89 vs. 4.25). More than 50% improvement was seen in 40% of group B patients and 20% of group A patient. MASI score in group A (with baseline value of 8.73) after the first follow-up and in week 4 was 6.95 (25.36%), it was 5.02 (42.5%) in the second follow-up and week 8, and it was 4.48 (48.69%) in third follow-up and week 12. In group B, MASI score (with baseline value of 9.27) was 6.74 (27.3%), 4.56 (50.81%), and 38(63.54%), respectively</p>

TABLE 1 (Continued)

	Title, year, and type of trial	Number of the participants, type of melasma, and type of needling	Treatment arms and distances	Efficacy, side effects, and reliability of treatment
7	A Face-Split Study to Evaluate the Effects of Microneedle Radiofrequency with Q-Switched Nd:YAG Laser for the Treatment of Melasma Jung et al (2019) 5 authors Case report ²¹	Participants: There were fifteen patients (14 females and 1 male) with melasma and a mean age of 43.1 years old. Two patients had Fitzpatrick type III and 13 had Fitzpatrick type IV. Method: A microneedle RF device with minimal invasion and 25 uninsulated bipolar electrodes (5.5 parallel rows) was used	All patients underwent 5 sessions of microneedle RF and 1064 nm QSNY low current laser treatment on the right side of their face and only 1064 nm QSNY low current laser treatment on the left side with a 2-week interval between treatment sessions. Prior to treatment, 2.5% lidocaine and 2.5% prilocaine cream were applied on the lesions. Patients were treated with QSNY laser at a low speed of 1064 nm (PTP mode, fluorescence J / cm ² 1.19, spot size 8 mm) on both sides of their face to reach the end point of mild erythema. Then, fractional RF microneedles (intensity 50%, depth 1 mm, pulse duration 50 ms, single pass) were performed on the right side of the face on the same day. Patients were instructed to use a broad-spectrum sunscreen on their face. PSI score was used to evaluate the treatment outcomes	Both treatments showed a significant decrease in PSI score after five sessions. PSI score for combination therapy after the third visit was 7.90 (22.5% reduction) and after the sixth visit was 5.50 (46.1% reduction). PSI score for laser treatment was 9 (19.1% reduction) and 7.63 (31.4% reduction), respectively. Combined therapy showed a significant improvement in melasma compared to laser therapy. No significant side effects were reported.

(Continues)

TABLE 1 (Continued)

	Title, year, and type of trial	Number of the participants, type of melasma, and type of needling	Treatment arms and distances	Efficacy, side effects, and reliability of treatment
8	<p>Early clinical and histological changes induced by microneedling in facial melasma: A pilot study Cassiano et al (2019) 5 authors A quasi-experimental trial²²</p>	<p>Participants: Twenty women with facial melasma were evaluated at baseline (T0) and 7 days after the first treatment session (T7). Participants were divided into two groups of control (10 patients with a mean age of 43.3 years) and microneedling (10 patients with a mean age of 42.6 years).</p> <p>Type II skin phototypes: 0 in microneedling group and 2 (20%) in control group</p> <p>Type III: 7 patients (70%) in the microneedling group and 5 patients (50%) in the control group.</p> <p>Type IV: 3 patients (30%) in the microneedling group and 3 patients (30%) in the control group</p>	<p>The first ten patients were assigned to the microneedling group and a sampling (3 mm punch) of facial melasma lesions was obtained. Then, one microneedling session was performed using a 1.5 mm length needle. After 1 week, the microneedling group underwent new sampling. All patients used sunscreen (SPF 50). MASI scoring was used to assess the severity melasma</p>	<p>MASI score in microneedling group increased from 4.5 to 4.1 (decrease of 8.89%) and for control group from 6 to 6.2 (increase of 3.33%)</p>

TABLE 1 (Continued)

9	Title, year, and type of trial	Number of the participants, type of melasma, and type of needling	Treatment arms and distances	Efficacy, side effects, and reliability of treatment
	<p>Comparative assessment of microneedling with or without drug delivery in melasma treatment</p> <p>Agostinho et al, 2019</p> <p>5 authors</p> <p>A randomized clinical trial²³</p>	<p>Participants: there were 20 participants divided into two groups.</p> <p>Group A: 7 patients were treated with microneedling only.</p> <p>Group B: 13 patients received lightening serum delivery in three sessions at monthly intervals after microneedling.</p> <p>Method: Microneedling was performed with a 7 × 7 mm gold-plated microneedling device from the Solon[®] platform with radio frequency: 0 W, pulse duration: 80 ms, needle depth 1.5 mm</p>	<p>One hour before each procedure, local anesthesia (lidocaine and tetracaine cream 7.7%) was performed on the whole face.</p> <p>For group A, microneedling was performed in three sessions with an interval of 30 days. Group B also underwent microneedling.</p> <p>In the patients of this group, drug delivery was done immediately after microneedling, which included topical application of 0.8 ml of MD: melanoceuticals industrial whitening product. This product was a combination of kojic acid, tranexamic acid, azelogylicine, arbutin, glycolic acid, ascorbic acid, citric acid, and glutathione in unknown concentrations.</p> <p>Patients were instructed to use sunscreen (SPF 60) 24 h after surgery. MASI scoring was used</p>	<p>The group that received microneedling with drug delivery had better results in recovery. Improvement of MASI was similar in both groups. There was an 85.71% decrease in MASI score for group A and a decrease of 84.62% for group B</p>

(Continues)

TABLE 1 (Continued)

	Title, year, and type of trial	Number of the participants, type of melasma, and type of needling	Treatment arms and distances	Efficacy, side effects, and reliability of treatment
10	A Split Face Comparative Study of Safety and Efficacy of Microneedling with Tranexamic Acid versus Microneedling with Vitamin C in the Treatment of Melasma Menon et al, 2020 5 authors A split face comparative study ²⁴	Participants: 30 women with bilaterally symmetrical melasma who aged between 18 and 55 years were recruited. Seventeen patients had Fitzpatrick type 5 (56.7%) and 13 patients had type 4 (43.4%). Method: Microneedling was performed in vertical, horizontal, and diagonal directions. The dermaroller had 192 microneedles made of first-class medical stainless steel with a width of 2 cm and a needle with 1.5 mm length and a diameter of 0.25 mm	After microneedling, 1 ml TXA (4 mg / ml) was applied on the left side and 20% vitamin C on the right side of patients' face. The procedures were performed twice over a one-month interval (week 0 and week 4). MASI was used to assess the severity melasma	MASI score improved 8.9% (from 8.93 to 8.2) after 4 weeks' treatment with TXA and 3.7% (from 8.93 to 8.6) following treatment with vitamin C. At the end of 8 weeks, 20.5% improvement was observed with TXA and 12.3% with vitamin C. No serious side effects were observed

TABLE 1 (Continued)

11	Title, year, and type of trial	Number of the participants, type of melasma, and type of needling	Treatment arms and distances	Efficacy, side effects, and reliability of treatment
11	Study of efficacy of microneedling and mesoneedling in the treatment of epidermal melasma: A pilot trial Farshi and Mansouri (2020) 2 authors open pilot trial ¹⁵	Participants: 20 patients (1 male and 19 female) with Fitzpatrick type III (79%) and IV (30%) who aged between 18 and 50 years old were recruited. Method: Amiea Med was used for microneedling, while mesoneedling was performed by mesenchymal injection solution. The length of the needle was 1.5 mm and its diameter was 0.25 mm. The needles penetrated the skin from 0.1 to 1.3 mm	The four monthly treatments given to all patients included microneedling on one side and mesoneedling on the other side of their face. Local anesthesia was performed. The treatment was performed by rolling the cylinder back and forth approximately four times in all four directions (right, left, and horizontal-vertical), which resulted in diffuse erythema and intermittent bleeding. Microneedling and mesoneedling were performed in 2 and 4 sessions, respectively. Patients were instructed to apply a standard sunscreen with a sun protection factor of ≥ 50 over their entire face and to repeat the program at 3-hour intervals throughout the day. Clinical evaluations were performed initially, at month 2, and at the end of the study (after 4 months). MASI scoring was used to assess the severity melasma	The mMASI scores obtained at the end of treatment were significantly lower in microneedling and mesoneedling groups. MASI score for microneedling was 11.37 before treatment, 8.99 after two sessions (20.94% reduction), and 8.05 after 4 sessions (29.2% reduction). MASI score for mesoneedling was 11.43 before treatment, 8.44 after two sessions (26.19% reduction), and 6.86 after 4 sessions (39.99%). These two methods were effective in treating melasma without any side effects or significant side effects.

(Continues)

TABLE 1 (Continued)

	Title, year, and type of trial	Number of the participants, type of melasma, and type of needling	Treatment arms and distances	Efficacy, side effects, and reliability of treatment
12	Microneedling versus fractional carbon dioxide laser for delivery of tranexamic acid in the treatment of melasma: A split face study Mekawy et al (2020) 3 authors Case report ¹⁶	Participants: 30 women with bilateral symmetrical facial melasma who aged >18 years' old Method: Microneedling was performed using Dr Pen with 12 needles. Needles length was proportional to the thickness of the skin and the location of the melasma lesion (0.25–1 mm). This method involved a combination of horizontal, vertical, and diagonal directions. Laser therapy: Power 8–10 watts (depending on skin type), distance 1000 micrometers (3.5 density), residence time 400 microseconds and stack 1. During the treatment session, protective eyewear was used by both the patient and the doctor	Use local anesthesia before treatment Patients were treated with fractional CO2 laser for one side of their face, and microneedling for the other side. This was followed by an immediate topical treatment with TXA solution of 4 mg/ml. Patients received six treatment sessions at two-week intervals. After treatment, patients were not allowed to use any face bleach cream or melasma treatment. They were also instructed to use a moisturizer, avoid sun exposure, and use sunscreen regularly. Treatment sessions were repeated at two-week intervals for six sessions. MASI scoring was used to assess the severity melasma	Two weeks after the last session, a significant decrease in the level of corrected melasma and mMASI was observed on both sides. Mean mMASI for microneedling and fractional CO2 laser-treated reduced from 3.34 to 1.59 (mean reduction 57.73, $p < 0.001$) and from 1.84 to 1.78 (mean reduction 55.82, $p < 0.001$), respectively. No statistically significant differences were observed between the two groups.

the breakdown time is reduced and the healing process is accelerated.¹⁵ It also induces matrix metalloproteinases, thereby reducing hyperpigmentation (Menon). In general, the efficiency, safety, and ease of use make microneedling a suitable treatment option.¹⁵ In an open trial, Lima et al. reported a significant reduction in MASI score from 37.1 to 11 (70% reduction in MASI) after two microneedling sessions.¹⁹ In addition, in a pilot study on 20 patients with melasma, it was shown that microneedling combined with topical depigmenting agents was more effective than topical depigmenting agents alone. In the aforementioned study, combined microneedling and depigmenting serum were applied on one side of the patients' face. The mean MASI score was significantly higher in the side treated with combined treatment than the other side of patients' face for which depigmenting serum alone was used. In addition, the mean MASI score increased from 19.1 to 9.2 for the patients' face side treated with microneedling after two months of treatment, while the mean MASI score decreased from 20.4 to 13.3 for the other side.¹³ In a case report study, the findings showed that the use of microneedling or fractional CO2 laser followed by topical application of TXA

resulted in a significant improvement in facial melasma. However, there was no statistically significant difference between the two groups in terms of mean mMASI reduction, degree of improvement, patient satisfaction, or the rate of development of side effects.¹⁶ However, Kown et al. showed that the mMASI score reduced 49.83% in the group treated with combined ND: YAG laser and fractional radiofrequency microneedling and only 32.78% in the group treated with ND: YAG laser alone.¹⁴ In a case report, Cameli et al. examined the effect of combined use of monopolar radiofrequency and transdermal drug delivery on 50 women with melasma and suggested this combination as a safe, effective, and non-invasive treatment for melasma.¹⁸ The findings of Farshi et al. show that the combination of Needling and Meso needling methods together is effective in increasing the improvement of treatment outcomes.¹⁴

Improvement in the treatment of melasma was also reported in a group treated with trans-epidermal delivery of tranexamic acid by microneedling.²⁰ The role of this drug on the improvement of melasma has been observed in many studies.^{25,26} In a review study by KIM et al., the efficacy and safety of tranexamic acid

TABLE 2 Cochrane Risk of Bias Tool Scale (kind of bias)

Other types of bias	Attrition bias	Reporting bias	Selection bias		Performance bias		
			concealment of Outcome	Concealment of participants	Random concealment	Random sequence generation	
Low	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Fabbrocini et al (2011)
Unclear	Low	Unclear	Low	Low	Low	Low	Cameli et al (2014)
Unclear	Low	Unclear	Unclear	Low	Low	Low	Lima (2015)
Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Lima et al (2017)
Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Kwon et al (2018)
Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Gupta et al, (2019)
Unclear	Low	Unclear	Unclear	Low	Low	Low	Jung et al (2019)
Unclear	Low	Unclear	Unclear	Unclear	Low	Low	Cassiano et al (2019)
Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Agostinho et al, 2019
Unclear	Low	Unclear	Unclear	Unclear	Low	Low	Menon et al, 2020
Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Farshi and Mansouri (2020)
Low	Low	Low	Low	Low	Low	Low	Mekawy et al (2020)

were evaluated in the treatment of melasma. They reported a decrease of 1.60 in MASI score following treatment. Minor side effects reported in this article were hypomenorrhea, mild abdominal discomfort, and transient skin irritation. They stated that tranexamic acid had good efficacy and safety, either alone or as an adjunct to conventional melasma treatments.²⁷⁻³² However, based on the present systematic study, an average decrease of 3.72 was observed in MASI score.

It seems that needling in various forms is effective for treatment of pigmentary disorders like melasma but its non-aggressive use as a micro-abrading instrument or just as a drug delivery improving device is enough for its evident benefit in melisma and aggressive use or obvious bleeding during procedure should be strongly avoided for this indication.

5 | CONCLUSION

Melasma is a chronic disease that is often resistant to treatment. Despite the various treatment options for melasma, fully controlling the condition and maintaining of the improvement therapeutic effect during the recovery period for a long time is still a challenge. Nevertheless, new treatments have been proposed for melasma, including techniques such as skin needling electroporation, sonophoresis, and iontophoresis, which are capable of transdermal drug delivery, increasing the absorption of local agents through the skin. Needling is an effective way to treat melasma. A systematic study of 12 clinical studies revealed that the use of needling therapy reduced the mMASI score by 85.71%. The mean decrease in MASI score was 3.72. Regarding the number of sessions, after two microneedling sessions, a significant decrease in MASI score was reported. The results showed that microneedling with topical depigmenting agents was more effective than topical depigmenting agents alone, so that the mean MASI score was significantly higher than those who used

depigmenting serum alone. However, the combined use of ND: YAG laser and fractional radiofrequency microneedling for the treatment of melasma, compared to the use of ND: YAG alone or the combined use of Monopolar Radiofrequency and Transdermal Drug Delivery can be a safe and effective non-invasive treatment for melasma.

However, short-term symptoms of treatment such as mild ulcers, hypomenorrhea, mild abdominal discomfort, and transient skin irritation were seen transiently, no side effects or recurrence after treatment was reported in reviewed articles. Therefore, it seems that a non-aggressive needling has a high efficiency and a few and acceptable side effects that make it an appropriate and effective option for the treatment of melasma.

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CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

All authors read and approved the final manuscript. ASB, EB, and NNN performed the research and drafted the paper and edited the final version. ASB and EB designed the study. MG, MR, and AG contributed in drafting the paper and acquisition of the data and editing the final version.

ETHICAL APPROVAL

None.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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