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Review Article

Is Tranexamic Acid Use Effective in Preventing Postinflammatory Hyperpigmentation after Laser Treatment? A Systematic Review and Meta-Analysis

Jiangfeng Feng,[1] **Sihao Shen**,[1] **Xiuzu Song**,[2] **and Wenzhong Xiang**[2]

[1]*Department of Dermatology, Hangzhou Third People's Hospital, Zhejiang Chinese Medical University, Hangzhou, China*
[2]*Department of Dermatology, Hangzhou Third People's Hospital, Affiliated Hangzhou Dermatology Hospital, Zhejiang University School of Medicine, Hangzhou, China*

Correspondence should be addressed to Wenzhong Xiang; xiangwenzhong@126.com

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Postinflammatory hyperpigmentation (PIH) is one of the most prevalent complications of laser treatment. However, comprehensive evidence is lacking to confirm the effect of tranexamic acid (TXA) for the prevention of postlaser PIH. We classified laser combined with TXA as the experimental group and laser alone as the control group from the selected studies in order to determine the efficacy of the extra use of TXA. We conducted a comprehensive literature review of randomized controlled trials (RCTs) that matched TXA coupled with laser vs. laser alone. The melanin index (MI) scores were employed as the clinically improved outcomes. Seven RCTs and a total of 222 individuals were evaluated in this meta-analysis. The findings revealed no statistically significant difference between the TXA and control groups in terms of decrease in mean MI scores at the end of the research ($P = 0.45$). The subgroup analysis showed that at month 1, extra use of TXA after laser treatment resulting in a statistically significant decrease in MI as opposed to laser alone ($P = 0.04$). However, at months 2 ($P = 0.73$), 3 ($P = 0.85$), and 6 ($P = 0.64$), the decrease in MI scores was not statistically significant. In addition, there was no statistically significant difference between topical, oral, and intradermal TXA on the reduction of MI scores after treatment ($P = 0.61$). Furthermore, nausea and menorrhagia occurred in the oral TXA group. The current meta-analysis found limited temporary efficacy of TXA in preventing postlaser PIH after 1 month.

1. Introduction

Postinflammatory hyperpigmentation (PIH) is a hyperpigmented skin condition succeeding skin inflammation, infection, allergic reactions, mechanical injury, or drug reactions [1]. PIH can cause considerable psychological stress and lower self-esteem for individuals affected, and treatment often takes longer to show results, with poor patient compliance [2].

Some photoelectric treatments, including carbon dioxide (CO_2), erbium-doped yttrium scandium gallium garnet, erbium-doped yttrium aluminum garnet (Er:YAG), and Q-switched Nd:YAG laser (QSNYL) will induce heat in the epidermis with the potential to induce PIH, which is manifested by a deepening of the skin color at the treatment site, even darker than the primary lesion [3]. Earlier research found that the incidence of PIH following 532-nm QS Nd:YAG laser therapy ranged from 6.7% to 53% in Asian patients [4]. In particular, the incidence of PIH after ablative fractional photothermolysis (AFP) was as high as 92% in Fitzpatrick skin type (SPT) IV patients [5].

Topical or oral agents such as glycolic acid, melatonin, hydroquinone, kojic acid, tranexamic acid, and cysteamine hydrochloride are considered the first-line treatment for hyperpigmentation [2]. However, using corticosteroids may cause erosions, infections, and poor wound healing [6]. Tranexamic acid (TXA) is a plasmin blocker that suppresses PGE2 and leukotrienes (LTs) through the plasminogen-plasmin pathway [7]. TXA inhibits melanogenesis by reducing tyrosinase proteins, TRP-2, and tyrosinase-related

protein (TRP)-1 [8]. According to a new study, TXA might decrease melanin formation by preventing the passage of the melanosome from melanocytes to keratinocytes [9].

There is no effective method to prevent PIH after laser treatment. Studies of TXA for preventing PIH after laser treatment are still being conducted on a small scale. As a result, we did a meta-analysis to evaluate the safety and efficacy of extra use of TXA for the prevention of PIH after laser treatment.

2. Materials and Methods

2.1. Strategy for Searching. We looked for Web of Science, Embase, Google Scholar, PubMed, and Cochrane Library databases for all related research investigations published up to 10 October, 2022 by means of the following search keyword "(laser ∗ AND (tranexamic acid ∗ (also known as TXA, TA, TNA, or antifibrinolytic agents) AND (hyperpigmentation ∗ OR pigmentation OR PIH)" in the article heading and abstracts. There were no language or publishing type limitations. There were no restrictions on the types of laser modes or parameter choices, usage of TXA, or the type of treated disease were applied.

2.2. Criteria for Inclusion and Exclusion. We identified studies suitable for inclusion in the present meta-analysis using the preset criteria listed as follows: (1) individuals who received RCTs, (2) individuals who received the laser combined with the extra use of TXA compared with the laser alone, and (3) individuals with melanin index (MI) scores employed as clinical enhancement outcomes. The following studies were not included: (1) comments, case reports, or reviews; (2) papers lacking the necessary data and cannot be concluded by contacting the corresponding authors or from available data; and (3) research that does not include humans.

2.3. Extraction of Data. For each investigation, two writers (FF and SS) extracted data separately. The major clinical enhancement outcome was the MI score. The year of publication, writer name(s), mean age or age range, research site, sample size, follow-up period, Fitzpatrick skin type, and intervention details were also provided. Any disagreements were settled via consensus. We also attempted to collect full data for certain investigations that lacked sample size by contacting the writers.

2.4. Evaluation of the Risk of Bias. Two authors (FF and SZ) assessed the risk of bias for each study according to the Cochrane Guide to Systematic Reviews [10], including allocation concealment, random sequence creation, blinding, insufficient information on results, selective reporting, and other biases. All inconsistencies were resolved through discussion among all authors.

2.5. Statistical Analysis. We calculated 95% confidence intervals (Cis) and standardized mean difference (SMZ) for the data using Review Manager 5.4 software. P values and the I^2 statistic were used to examine statistical heterogeneity. When $I^2 > 50\%$ or $P < 0.1$ and a random-effects model was employed, heterogeneity was found; however, a fixed-effects model was used. $P < 0.05$ was deemed statistically significant. Furthermore, a subgroup analysis was carried out on the degree of MI improvement in the four time periods, the method of TXA use, and the different laser modes. The assessment methodology has been registered on PROSPERO (CRD42022362872).

3. Results

3.1. Search Outcomes. A total of 174 similar papers were collected from 5 databases. After excluding duplicates and reviewing the abstracts and titles, 7 research investigations were incorporated into this meta-analysis. The technique for a literature search is displayed in Figure 1.

3.2. Features of the Research. All 7 RCTs were carried out in the Asian population. A total of 222 individuals participated in this meta-analysis, 56 for solar lentigines and 166 for melasma, with women accounting for 94.6% of all patients ($n = 210$). The participants varied in age from 18 to 70 years and had SPT type III–V. The period of follow-up lasted from the end of therapy to 6 months. TXA was utilized immediately after laser therapy in all investigations. Table 1 contains information about the included research. Specific TXA usage and laser parameters are shown in Table 2.

3.3. Bias Risk in Included Research. Figure 2 illustrates the quality rating of the 7 included investigations. Green dots denote low risk, whereas yellow dots denote unknown danger. Two research investigations did not indicate concealment of allocation, and one study did not provide information on participant blinding. Some information from three research investigations was not given in the paper. No high-risk studies were available.

3.4. The Outcomes of the Meta-Analysis. The MI score was utilized as the primary endpoint in seven studies. As Tawfic [11] studied the effects of both topical and intradermal injections of TXA, we divided it into two trials. We found no significant difference between the TXA and control groups in the seven studies in terms of mean MI scores reduction at the end of the last follow-up (SMZ = −0.08, 95% CI: −0.30 to 0.13, $P = 0.45$; Figure 3).

To assess the exact effect of TXA, we also conducted a comprehensive examination of the degree of improvement of MI compared to baseline at four posttreatment time periods: month 1 (SMZ = 0.42, 95% CI: 0.02 to 0.82, $P = 0.04$; Figure 4(a)), month 2 (SMZ = 0.06, 95% CI: −0.26 to 0.37, $P = 0.73$; Figure 4(b)), month 3 (SMZ = 0.04, 95% CI: −0.37 to 0.45, $P = 0.85$; Figure 4(c)), and month 6 (SMZ = 0.08, 95% CI: −0.26 to 0.42, $P = 0.64$; Figure 4(d)) after treatment. The subgroup analysis showed significant improvement in MI at month 1 with additional use of TXA in comparison to the control group.

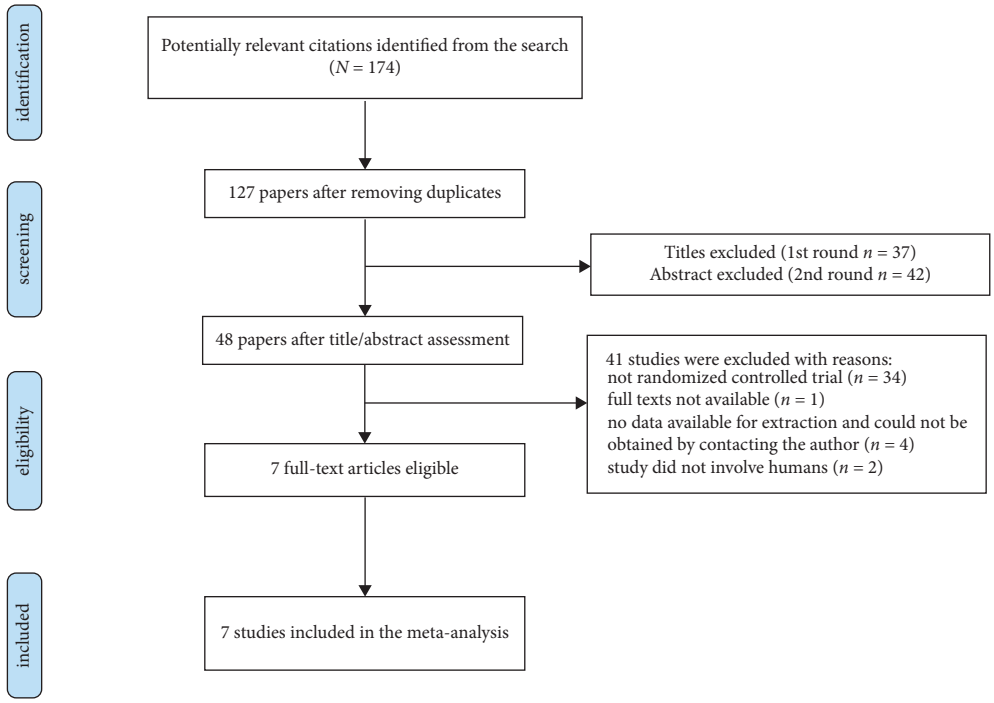


Figure 1: Meta-analysis flow diagram.

We also conducted a subgroup analysis of TXA usage to explore the effectiveness of different TXA administration modalities in the prevention of PIH after laser surgery (Figure 5(a)). However, there were no statistical significant differences between topical (SMZ = −0.13, 95% CI: −0.44 to 0.17, $P = 0.39$), oral (SMZ = −0.21, 95% CI: −0.65 to 0.23, $P = 0.36$), and intradermal (SMZ = 0.08, 95% CI: −0.34 to 0.49, $P = 0.72$) TXA.

To investigate the unique effect of various laser modes on PIH, for subsequent meta-analysis, we categorized fractional CO_2 laser and FTL as AFP, and QSNYL as nonablative fractional photothermolysis (NDR) (Figure 5(b)). The outcomes indicate that no statistically significant difference between AFP (SMZ = −0.08, 95% CI: −0.43 to 0.28, $P = 0.67$) and NDR (SMZ = −0.09, 95% CI: −0.36 to 0.19, $P = 0.55$).

3.5. Adverse Consequences. Mild erythema and searing pain were the most common adverse responses in the 7 research investigation examined because the discomfort generally disappear after the use of moisturizing and cooling skin creams. Though 2 investigations found that 6 individuals in the topical TXA group and 3 in the control group had PIH, possibly due to the additional inflammatory response produced by topical TXA. Two other studies reported that 6 people experienced nausea and 3 people had menorrhagia in the oral TXA group. No further adverse effects were noted, such as secondary bacterial infection, blistering, or bleeding.

4. Discussion

This meta-analysis includes 7 relevant RCTs that were incorporated to evaluate the safety and effectiveness of TXA in preventing PIH after laser treatment ($n = 222$); among them, melasma patients accounting for most of the cases ($n = 166$). Oral TXA is also one of the first-line therapies for melasma and significantly improved Melasma Area Severity Index (MASI)/modified MASI scores in melasma patients [18]. However, MI scores of melasma patients were not significantly reduced by oral or topical TXA treatment alone, in addition to intradermal TXA. Furthermore, there was no difference in MI in melasma patients treated with TXA alone compared to placebo and conventional treatments such as hydroquinone, Q-switched Nd : YAG laser, fractional thulium fiber laser, and fractional CO_2 laser [19]. Therefore, we believe that the change in the MI score is less affected by the reduction in melasma's original pigmentation in TXA coupled with laser vs. laser alone. The MI score is utilized to assess the seriousness of PIH [13]. The measurement of MI is based on the principle of spectral absorption, and the amount of melanin is determined by reflectance spectrophotometry to measure the amount of light reflected at a specific wavelength after shining on the skin [20].

The findings of the subgroup investigation indicate that extra use of TXA in laser treatment reduces MI after laser treatment by week 4, corresponding to the time of maximum occurrence of PIH in clinical practice [21]. Kang et al., in 2016, demonstrated that PIH was most noticeable at 4.3 weeks following the cure of solar lentigines with a 532-nm QS Nd:YAG laser, and that the PIH lasted for 2–24 weeks [22]. In a 2010 study of an Asian population, Chan et al. stated that the incidence of PIH induced after fractional ablative CO_2 laser treatment was the highest at week 4 [23]. Furthermore, Park et al. [24] discovered that using an epidermal growth factor cream following QS 532-nm Nd: YAG laser therapy dramatically decreased MI and the frequency of PIH on day 35.

Table 1: Characteristics of the included studies.

Study (year)	Country	Treated diseases	Treated area	Mean age or age range (Y)	SPT	F/N	Follow-up time (m)
Tawfic et al. (2019) [11]	Egypt	Melasma	Face	39.61 ± 6.71	III–V	28/28	6
Wanitphakdeedecha et al. (2020) [12]	Thailand	Melasma	Face	48.00 ± 10.00	III–V	44/46	6
Sirithanabadeekul and Srieakpanit (2018) [13]	Thailand	Solar lentigines	Forearm	60.88 ± 6.64	III–V	18/25	3
Laothaworn and Juntongjin (2018) [14]	Thailand	Melasma	Face	44.79 ± 7.79	III–V	24/25	2
Rutnin et al. (2019) [15]	Thailand	Solar lentigines	Forearm	18–70	II–V	38/40	3
Shin et al. (2013) [16]	Korea	Melasma	Face	18–55	III-IV	48/48	2
Laothaworn et al. (2016) [17]	Thailand	Melasma	Face	33–53	III–V	10/10	2

Y, years; m, months; F, female; N, total number of patients; SPT, Fitzpatrick skin type.

Table 2: TXA application and laser parameters of the included studies.

Study	TXA application			Laser parameters					
	Usage	Dosage or concentration	Times/ duration	Laser modality	Wavelength	Spot size or scanning area	Output power or fluence	Times	Interval time
Tawfic et al. (1)	Topical	10%	Once	Fractional CO_2 laser	10,600 nm	NM	12 Watts	5	4–6 w
Tawfic et al. (2)	Injection	100 mg	Once	Fractional CO_2 laser	10,600 nm	NM	12 Watts	5	4–6 w
Wanitphakdeedecha et al.	Topical	1.2%	Once	FTL	1,927 nm	100 μm	5 mJ	4	1 w
Sirithanabadeekul and Srieakpanit	Injection	1.5 mg	Once	QSNYL	532 nm	1.8 mm	0.6–0.8 J/m^2	1	NM
Laothaworn and Juntongjin	Topical	3%	Once daily/8 w	QSNYL	1,064 nm	6 mm	2.0–3.0 J/ cm^2	2	4 w
Rutnin et al.	Oral	1500 mg	Twice daily/6 w	QSNYL	532 nm	3 mm	1.8–2.3 J/ cm^2	1	NM
Shin et al.	Oral	750 mg	Twice daily/8 w	QSNYL	1,064 nm	7 mm	2.0 J/cm^2	2	4 w
Laothaworn, et al.	Topical	NM	Once	QSNYL	1,064 nm	NM	NM	2	4 w

QSNYL, Q-switched Nd : YAG laser; FLT, fractional thulium fiber laser; w, weeks; NM, not mentioned.

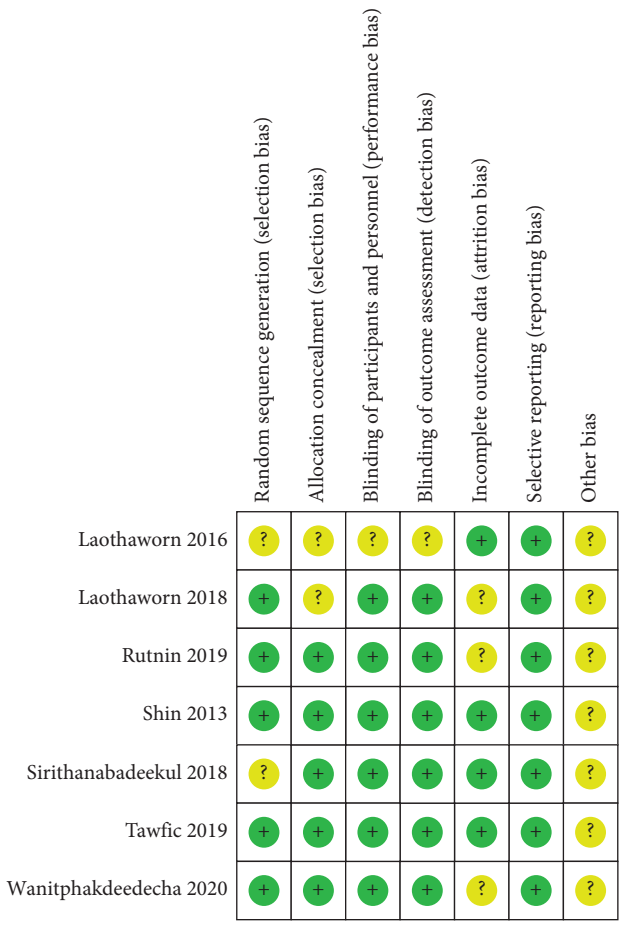


Figure 2: Risk of bias summary.

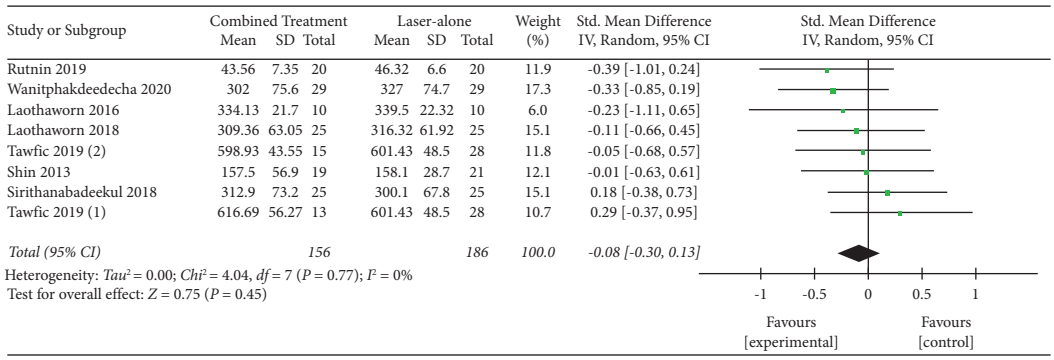


Figure 3: Forest plot compares the MI score variations between combined therapy and laser treatment alone.

TXA has been extensively employed in the therapeutic treatment of pigmented dermatoses, and it can be administered through topical, intradermal injection, microneedle, oral, or iontophoresis [25]. Though the outcomes of the subgroup analysis presented no significant differences between TXA dosing regimens in the prevention of PIH, although all three TXA dosing regimens—oral, topical, and intradermal—showed a decrease in MI at the end of treatment compared to baseline. Different drug delivery methods have different advantages and disadvantages. Orally given TXA has only 30–50% bioavailability [7] and may increase the risk of gastrointestinal distress, thromboembolism, myocardial infarction, and pulmonary embolism [26]. Our results also show that two studies reported that six patients experienced nausea after taking TXA. Moreover, poor treatment adherence may result in inefficient PIH prophylaxis of oral TXA. Topical TXA is relatively safer than oral administration; however, at higher concentrations, it can cause adverse reactions such as skin irritation and peeling [2]. Tawfic et al. [11] showed a lower rate of improvement in MI with topical TXA combined with a laser than in the laser alone group, possibly due to an

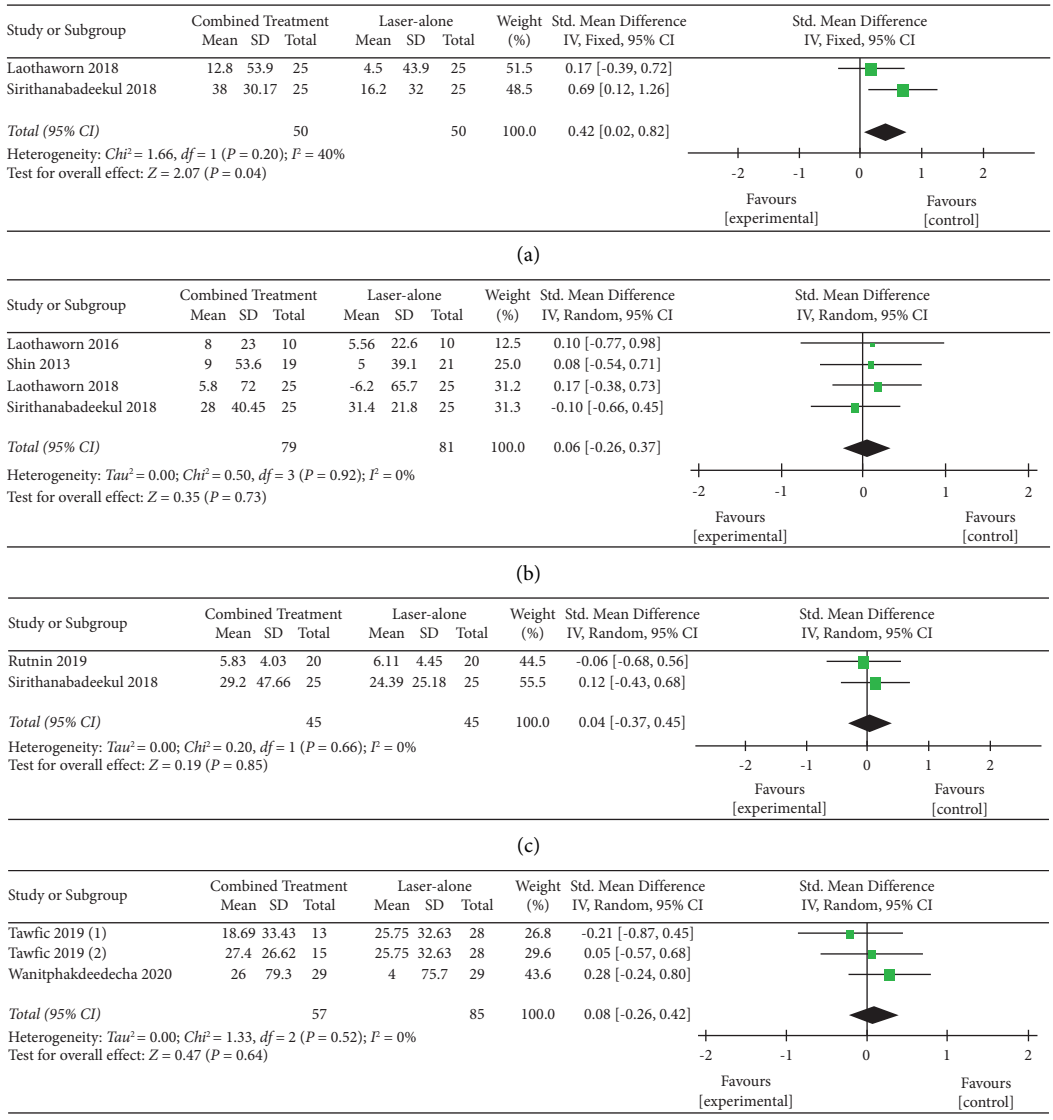
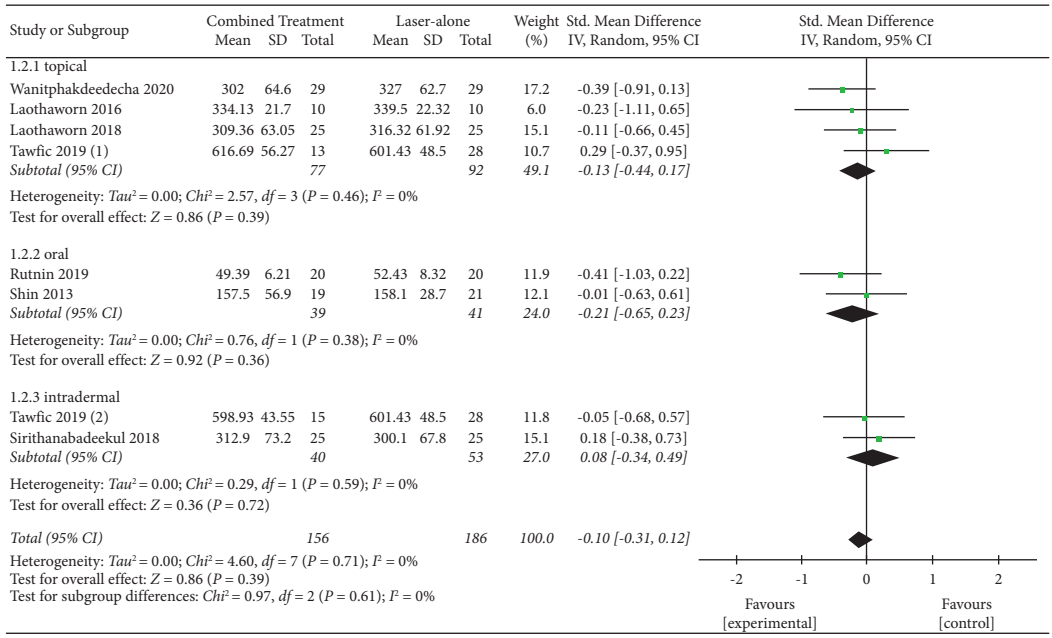


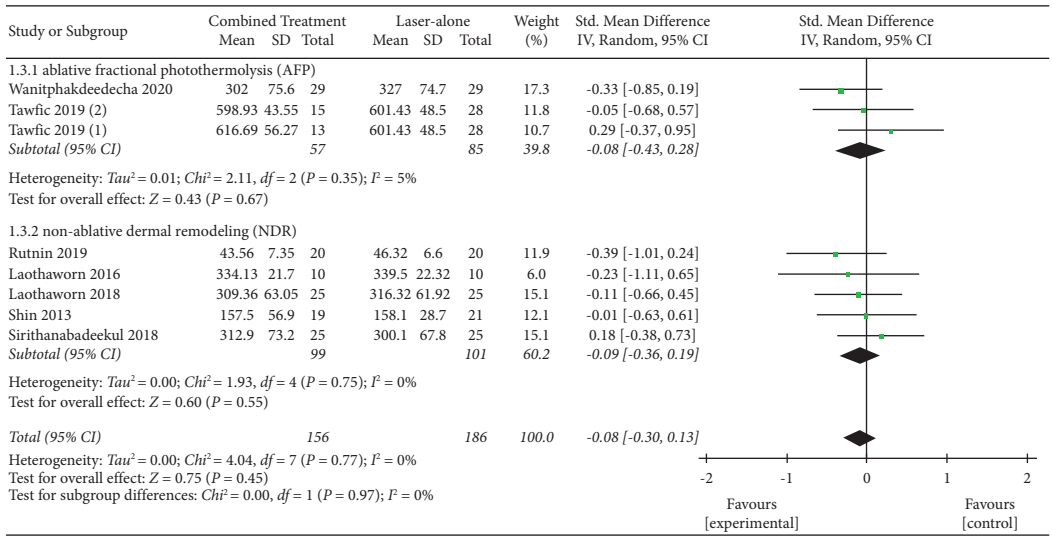
Figure 4: Forest plot showing comparison of the degree of reduction in MI scores compared to baseline at (a) 1 month, (b) 2 months, (c) 3 months, and (d) 6 months after laser treatment.

additional inflammatory response from topical TXA immediately after laser surgery. Intradermal TXA has a high bioavailability. The pathogenesis of PIH develops in the dermal and epidermal layers of the skin, and medicines administered intradermally can be distributed across these layers [27]. However, intradermal TXA may also aggravate the primary disease and produce additional inflammation. Therefore, topical or intradermal application of tranexamic acid should be alternated with laser treatment rather than immediately after laser treatment and may reduce the additional inflammatory response triggered when the two modalities are combined.

Fractional CO_2 lasers and FLT are AFP modalities. The microepidermal necrotic debris (MEND) extruded after fractional pyrolysis contains melanin, which is then excreted through the stratum corneum, causing depigmentation of the epidermis and dermis [28]. Furthermore, there is a redistribution of melanin between treated and untreated skin, which leads to a decrease in the hyperpigmented look of the skin overall [29]. The QSNYL, an NDR laser, is routinely used to cure melasma and has had great results [30]. The QSNY, based on the subcellular selective photothermolysis hypothesis, enables the laser to enter the dermis and target melanin, with the absorbed energy selectively eliminating melanin while causing little damage to the surrounding tissue [31]. However, both AFP and NDR lasers may lead to PIH [32]. In darker skin types, inducing heat in the epidermis can potentially exacerbate melasma or induce PIH. Inflammatory mediators produced by laser-induced keratin-forming cell damage, including thromboxane B2, prostaglandin D2, prostaglandin E2 (PGE2), leukotriene C4, leukotriene D4, leukotriene B4, and leukotriene E4, can upsurge melanin synthesis, induce dendritic cell proliferation, and increase melanocyte size, thereby leading to



(a)



(b)

Figure 5: Forest plot compares the MI score variations (a) between topical, oral, and intradermal use of TXA and (b) between ablative fractional photothermolysis (AFP) and nonablative fractional photothermolysis (NDR).

PIH [1]. Our subgroup analysis also indicated no statistically significant difference between the laser modalities of AFP and NDR used for treatment regarding the decrease in mean MI scores.

5. Conclusion

This meta-analysis found a statistically significant decrease in MI scores in the first month with the extra use of TXA after laser treatment compared to laser alone. However, there was no statistically significant decrease in MI scores at months 2, 3, and 6. There was also no significant difference in the decrease in MI scores between methods of TXA use and between laser modalities. Furthermore, our review indicated that oral TXA may increase the risk of developing nausea and menstrual irregularities, and frequent topical TXA application after laser treatment may increase additional inflammatory responses. Therefore, a 1-month course of topical or intradermal TXA may prevent PIH after laser treatment while avoiding excessive inflammatory reactions and side effects. More large-scale RCTs are required to offer comprehensive information on TXA usage and treatment duration to help find ways to prevent PIH after laser treatment.

5.1. Limitations. First, the patients included in our research investigation had different types and severity of pigmentary disorders. Second, there is a wide age distribution of

patients, which may result in variations in facial metabolic capability. Third, the sample sizes for the first, second, third, and sixth months were still insufficient due to the insufficient number of studies, resulting in insufficient statistical power. For that reason, additional RCTs are necessary to verify the effectiveness of TXA in preventing PIH after laser treatment.

Data Availability

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

Ethical Approval

This research did not include any human subjects.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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