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Comparing the efficacy of Myjet-assisted tranexamic acid and vitamin C in treating melasma: A split-face controlled trial

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Abstract

Background: Melasma is a benign and chronic hypermelanosis characterized by irregular light brown to dark brown patches of hyperpigmentation on the skin. Oral tranexamic acid (TA) or vitamin C (VC) supplementation has been one treatment choice. TA interferes with keratinocyte-melanocyte interactions, and VC functions by reducing melanin production resulting in skin rejuvenation and whitening.

Aim: The aim of the present study was to compare the efficacy and safety of Myjet assisted transdermal injection of TA vs VC in the treatment of melasma.

Methods: In this split-face controlled trial, 17 patients were randomized to receive eight weekly transdermal injections of TA or VC via Myjet either on the right or the left side of their face. MASI was measured from each side of the face at the baseline, at the middle, and at the end of treatment.

Results: A reduction in MASI was observed for TA and VC separately (*P* value < 0.05). The difference in efficacy between TA and VC group was not statistically significant (P value 0.05). Both treatments were well tolerated, with no serious adverse events reported.

Conclusion: Weekly TA or VC transdermal injections can be an effective treatment for melasma. Further studies are required to validate these findings.

KEYWORDS
meliasma, tranexamic acid, transdermal injection, vitamin C

1 | INTRODUCTION

Melasma is an acquired, benign, and chronic hypermelanosis characterized by irregular light brown to dark brown patches of hyperpigmentation on the skin. Its prevalence varies according to ethnic background, skin phototype, and intensity of sun exposure.[1] The precise incidence of melasma remains unknown but both males and females can be affected in nearly every racial subgroup. Melasma is more common in darker skin types, particularly Fitzpatrick skin types III and IV, and often lasts for many years after pregnancy.[2] Melasma appears as light brown to dark, muddy brown macules and patches on the face, especially the forehead, malar areas, and chin, and it may last for decades, impacting on quality of life in those affected patients, such as emotional well-being and social life.[3] Interestingly, the negative effect on quality of life with melasma such as depression was not correlated with the severity of melasma, suggesting that even a small amount of pigmentation may have a significant emotional role.[2] The pathogenesis of melasma is complex, and its treatment remains challenging. While sun exposure, pregnancy and oral contraceptives are thought to be risk factors, much remains to be elucidated.[4] Therapeutic innovation for melasma remains a goal for dermatologists worldwide.

There are many treatment options for melasma, including topical drugs, oral drugs, chemical peels, and laser and light treatments.[5]

Topical hydroquinone has been the gold standard for the treatment of melasma for a long time, but in the recent years, due to its demonstrated efficacy and rarity of side effects, oral tranexamic acid (TA) has begun to emerge as the possible new standard therapy for melasma treatment.[6] In the past, TA, a synthetic derivative of the amino acid lysine, was a kind of hemostatic drug. The exact mechanism of action of TA in the treatment of melasma is not completely understood. TA displays both anti-plasmin and anti-inflammatory properties.[7] Clinical trials have proven that oral TA is an effective and safe therapy for the treatment of melasma.[8] Clinical response was usually observed after 1-2 months.[8-10]

Vitamin C inhibits melanin formation and reduces oxidized melanin, and systemic VC supplementation has been an effective alternative for treatment of melasma.[11] Chemical peeling is an adjunctive treatment modality for melasma due to its ability to increase keratinocyte turnover, increase epidermal remodeling, and increase pigment metabolism.[5] Moreover, many laser energy sources (such as Q-switched Nd: YAG, IPL) have been used and laser therapy has been investigated to treat melasma with varying clinical efficacy.[12-14]

Myjet (Myjet, TavTech) is a new device for facial rejuvenation and promoting transdermal absorption of topical drugs.[15] The Myjet can be described as using a mixture of water and oxygen forced into a channel, which accelerates the droplets through a specific nozzle at approximately 200 m/sec speed, delivering a powerful flux of microdroplets into the skin.[15,16] It is a safe and painless medical device which can be used for transdermal drugs absorption, skin cleaning, and dermoepidermal hydration. Moreover, it has been applied to treat androgenetic alopecia, hyperhidrosis, and fine wrinkles in clinical practice.[16,17]

The aim of this original research was to compare the efficacy and safety of Myjet-assisted transdermal injection of TA vs VC in the treatment of melasma.

2 | MATERIALS AND METHODS

2.1 | Participants

This was a single-center, prospective, split-face, randomized, double-blind study comparing the efficacy of Myjet-assisted TA and VC in the treatment of melasma. Altogether, 17 patients (1 male and 16 females) with bilateral symmetric facial melasma treated at the Plastic Surgery Hospital, CAMS&PUMC, Beijing, China between December 2017 and August 2018 were enrolled; including thirteen patients with Fitzpatrick skin type III and four patients with Fitzpatrick skin type IV, all had a clinical diagnosis of melasma. Each patient was randomized to receive TA and VC transdermal injection by Myjet either on the right or the left side of their face. Exclusion criteria included underlying chronic or inflammatory systemic disease, photosensitivity, pregnancy, breastfeeding, chemical peeling, and laser treatment history in latest six months. This study was approved by the Ethics Committee of Plastic Surgery Hospital, Chinese Academy of Medical. All the participants provided informed consent.

2.2 | Materials and procedures

At baseline, medical history was taken for each patient including demographic data, history of sun exposure and pregnancy, duration of melasma. Wood's light examination was used to categorize melasma according to the depth of melanin pigment into epidermal, dermal, and mixed. By performing simple randomization through random number generation, treatment decisions were made about split-face treatment side.

Localized Myjet-assisted injection of TA (0.5 g:5 mL; Salvage pharmaceutical co) and VC (1 g:2.5 mL; Huarun shuanghe pharmaceutical co) were applied on one side of the face by a trained dermatologist for eight sessions at one-week intervals.

After cleansing the face with water and facial cleanser, the doctor used normal saline, assisted by Myjet (Myjet, TavTech), to clean the entire face three times. The distance between the handpiece and skin was 5, 3, and 1 cm each time, and the angle between the handpiece and skin was 45 degrees. Distilled water was then used twice to clean the residual saline at a 45 degrees angle and 1 cm distance. TA and VC were transdermally injected by Myjet on either the right or the left side of the face, respectively. The Myjet handpiece was held vertical to the skin at a distance of 0.5 cm. The dosages of both TA and VC for each side did not exceed 2 mL per week. The duration of treatment was two months, and during that time, patients were instructed to apply an SPF 50 plus sunscreen before daily activities.

2.3 | Clinical assessment

Evaluation of treatment efficacy was based on clinical observations and photographic evaluations. The assessment of patient response was based on the hemi-MASI score of the right and left side independently by two experienced dermatologists. Evaluation was done at the beginning of treatment, at the end of fourth week, and one week after the last treatment session.

$$\text{hemi - MASH} = 0.15\,(D + H)\,A\,(\text{forehead}) + 0.3\,(D + H)\,A\,(\text{malar}) + 0.05\,(D + H)\,A\,(\text{chin}).$$

where D is darkness, H is homogeneity, and A is area.

The darkness of melasma (D) was compared to the normal skin and graded on a scale of 0-4 as follows:

- 0 = normal skin color without evidence of hyperpigmentation;
- 1 = barely visible hyperpigmentation;
- 2 = mild hyperpigmentation;
- 3 = moderate hyperpigmentation;
- 4 = severe hyperpigmentation.

Homogeneity of hyperpigmentation (H) was also graded on a scale of 0-4:

- 0 = normal skin color without evidence of hyperpigmentation;
- 1 = specks of involvement;

TABLE 1 Patient demographic and baseline clinical information

Item	Number
Age (y) mean ± SD	39.47 ± 6.05
Gender	
Female	16
Male	1
Fitzpatrick skin type	
III	13
IV	4
Duration of melasma (y) mean ± SD	6.24 ± 3.97
Melasma type, number	
Epidermal	5
Dermal	6
Mixed	6
Trigger factors, number	
Pregnancy	3
Sun exposure	5
Others	6

- 2 = small patchy areas of involvement with a diameter of 1.5 cm and below;
- 3 = patches of involvement with a diameter of 2 cm and above;
- 4 = uniform skin involvement without any clear areas.

Area (A) was assigned for the percentage of involvement as follows:

- 0 = no involvement;
- 1 ≤ 10% involvement;
- 2 = 10%-29% involvement;
- 3 = 30%-49% involvement;
- 4 = 50%-69% involvement;
- 5 = 70%-89% involvement;
- 6 = 90%-100% involvement.

Standardized digital images taken with a digital camera (Cannon EOS 750D) and VISA pictures by Visa System (Canfield Scientific Inc) were taken at baseline, at the end of fourth week, and one week after the last session. Patients were also asked to report their degree of pain, discomfort, postinflammatory hyperpigmentation (PIH), and erythema on each side of their face throughout the study period.

Improvement in melasma was evaluated as follows: (a) Excellent: melasma area decreased by 90% or hyperpigmentation almost vanished; (b) Good: melasma area decreased by 60% or significant reduction of hyperpigmentation; (c) Fair: melasma area decreased by 30% or visible reduction of hyperpigmentation; and (d) Poor: melasma area decreased less than 30% or no visible reduction of hyperpigmentation.

After eight treatment sessions, patients were asked about their degree of satisfaction: highly satisfied, moderately satisfied, fairly satisfied or not satisfied.

TABLE 2 Changes in hemi-MASI after topical TA and VC application

	Hemi-MASI					
	Baseline		1st follow-up[a]		2nd follow-up[b]	
Patient	TA	VC	TA	VC	TA	VC
1	2.7	2.7	2.7	2.7	0.6	0.6
2	1.2	0.6	1.2	0.6	1.2	0.6
3	6.0	6.0	2.4	2.4	1.2	1.2
4	3.0	3.0	1.5	1.5	1.2	0.6
5	12.3	10.8	9.0	7.8	4.8	6.0
6	7.2	3.6	2.4	2.4	0.6	0.6
7	10.2	14.4	10.2	13.2	3.9	5.4
8	2.5	2.5	2.5	2.5	2.5	2.5
9	8.4	9.0	5.6	6.0	2.4	3.9
10	2.4	1.8	1.8	0.9	0.6	0.6
11	4.2	3.6	3.9	3.6	1.2	0.6
12	7.2	9.6	7.2	9.4	3.6	1.8
13	9.9	7.5	4.8	4.8	1.2	1.2
14	12.3	12.3	9.3	9.3	5.1	5.1
15	10.5	10.5	10.2	7.8	7.8	7.8
16	12.3	12.0	12.0	12.0	9.0	12.0
17	7.2	8.1	5.4	6.3	3.6	6.0

Abbreviations: TA, tranexamic acid, VC, vitamin C.
[a]1st follow-up: at the end of fourth week.
[b]2nd follow-up: 1 wk after the last session.

Adverse events, including erythema, scaling, erosion, itching, and burning, were recorded at each visit. Two months after the last session, the recurrence was also noted based on an increase of 20% or more in MASI scores.

2.4 | Statistical analysis

The SPSS17.0 software (SPSS) was used to analyze all data. An independent *t* test was used to compare baseline MASI scores. A paired-sample *t* test was used to compare MASI reductions from baseline at each treatment timepoint separately. Data were evaluated using statistical methods (mean, standard deviation, frequency, ratio, minimum and maximum). *P* value < .05 was considered statistically significant for analyses.

3 | RESULTS

Nineteen patients were initially enrolled, and seventeen patients completed the study after two had dropped out. The mean age of the study population was 39.47 ± 6.05 (ranged between 30 and 48 years of age). The demographic and baseline characteristics are shown in Table 1. Table 2 shows the changes in hemi-MASI after

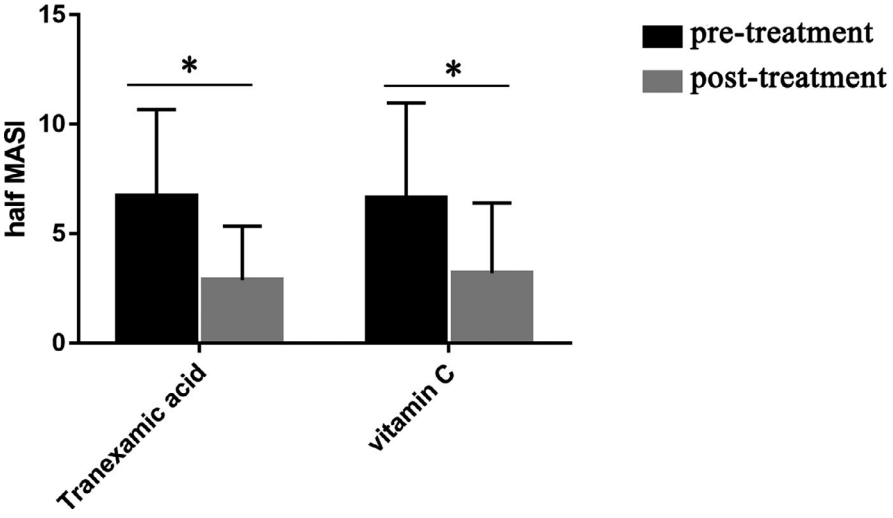

FIGURE 1 Change in hemi-MASI for tranexamic acid (TA) and vitamin C (VC) sides after treatment. *P < .05

topical TA and VC application. At baseline, there was no difference between the hemi-MASI on both sides (7.03 ± 3.84 vs 6.94 ± 4.28; P value = .950). The hemi-MASI mean value ± SD at baseline, end of 4th week, and one week after the last session were 7.03 ± 3.84, 5.42 ± 3.56, and 2.97 ± 2.53 for the TA side and 6.94 ± 4.28, 5.48 ± 3.91 and 3.32 ± 3.30 for the VC side, respectively. By considering the interventions separately, a significant reduction was observed for both sides (TA: 7.03 ± 3.84 vs 2.97 ± 2.53, P value = .001; VC: 6.94 ± 4.28 vs 3.32 ± 3.30, P value = .01; Figure 1, Table 3). Figure 2 illustrates the variation tendency of hemi-MASI during the treatment period. There was no significant difference between TA and VC treated sides regarding reduction in hemi-MASI (4.06 ± 2.62 vs 3.62 ± 2.79, P value = .638).

After two months of treatment, the results were as follows: excellent (0%, 0/17), good (70.6%, 12/17), fair (17.6%, 3/17), and poor (11.8%, 2/17). Thus, the total improvement rate for melasma was 70.6% among all subjects.

At the end of the treatment, 11 patients (64.7%) in the TA group and 10 patients (58.8%) in the VC group were at least satisfied with the final results. On the other hand, six patients (35.3%) in TA group and seven patients (41.2%) in VC group showed fair satisfaction or no satisfaction with the final results (Figure 3).

TABLE 3 Evaluation of treatment efficacy by hemi-MASI in TA and VC groups

	TA	VC	*P* value
Baseline (mean ± SD)	7.03 ± 3.84	6.94 ± 4.28	.950
1st follow-up (mean ± SD)	5.42 ± 3.56	5.48 ± 3.91	.960
2nd follow-up (mean ± SD)	2.97 ± 2.53	3.32 ± 3.30	.728
Baseline-2nd follow-up (mean ± SD)	4.06 ± 2.62	3.62 ± 2.79	.638

Abbreviations: TA, tranexamic acid, VC, vitamin C.
[a]1st follow-up: at the end of fourth week.
[b]2nd follow-up: 1 wk after the last treatment session.

Most patients showed clinical improvement with treatment (Figure 4 and Figure 5). Two patients reported mild erythema, and one patient felt stuffy during the injection process. These symptoms generally disappeared after approximately ten minutes. No other side effects were reported. At the two-month follow-up point, one case of recurrent melasma was observed; a 48-year-old housewife with Fitzpatrick skin type IV and no history of excessive sun exposure.

4 | DISCUSSION

Melasma is a chronic and common pigmentary disorder among Asian women, usually appearing as a symmetric facial condition characterized by irregular light brown to dark brown hyperpigmented patches. This condition is often psychologically distressing in affected patients. The predisposing factors for this disease are intricate, and its multifactorial pathogenesis remains to be elucidated.

Treatments for melasma include topical and oral drugs, chemical peels, as well as laser and light treatments. Treatment strategies are broken down into three levels: the first line is topical skin-depigmenting agents, or broad-spectrum sunscreens and camouflage, the second line is chemical peels, and the third line is the laser or light treatment.[18-20]

Tranexamic acid is a kind of hemostatic drug which can bind to lysine residues of plasminogen and prevents its conversion to plasmin. Furthermore, it can decrease the generation of arachidonic acid and α-melanocyte-stimulating hormone (α-MSH), resulting in reduction of pigment production in melanocyte.[21,22] A study by Kim et al[23] indicated that suppression of endothelin (ET)-1 could be one of the mechanisms of action of TA in melasma. Since, TA has been used more in recent years, there are many clinical trials to verify its effectiveness and safety. Lee et al[24] performed the first preliminary clinical trial on the efficacy of localized intradermal microinjection of TA in 2006, where they reported a significant decrease in the MASI at weeks 8 and 12 from the baseline. In 2012, Wu[8] and colleagues conducted a study which indicated that oral administration of TA was an effective

treatment for melasma and the initial reduction of pigmentation was usually observed after 1-2 months. Additionally, Najmolsadat et al[25] performed a randomized comparative study of topical tranexamic acid and hydroquinone in treatment of women with melasma; both groups showed improvement in the MASI score but there was no significant difference between the two groups. Nasrin et al[26] showed that monthly intradermal TA microinjection was an effective treatment for melasma. These studies show that oral administration, topical application, and microinjection of TA are effective. Notable adverse effects of oral TA include abdominal bloating, headache, tinnitus, menstrual irregularities, and, rarely, deep venous thrombosis (DVT).[21] DVT is a relatively serious adverse effect, and patients with risk of blood clots should not receive systemic TA.

Application of topical VC is very common in the daily care of melasma, other pigment disorders and skin whitening. VC is effective in reducing melanin formation by interacting with copper ions at the tyrosinase-active site that leads to inhibition of tyrosinase enzyme.[27] Several trials on the effect of VC on treating melasma have been reported. Lee et al[28] demonstrated significant improvement with ultrasonic application of VC compared to laser monotherapy. In 2017, Pelin et al[14] compared the efficacy and safety of Q-switched Nd:YAG laser plus microneedling with vitamin C and Q-switched- Nd:YAG laser alone, including sixteen patients with recalcitrant melasma, suggested that VC application with microneedling immediately after treatment with Q-switched Nd:YAG laser for four sessions at four-week intervals is a promising adjunctive method for the treatment of recalcitrant melasma. In another study, Ismail et al[29] reported thirty female patients with melasma received six sessions of microneedling with addition of topical VC every two weeks, all patients showed improvement at the end of the sessions.

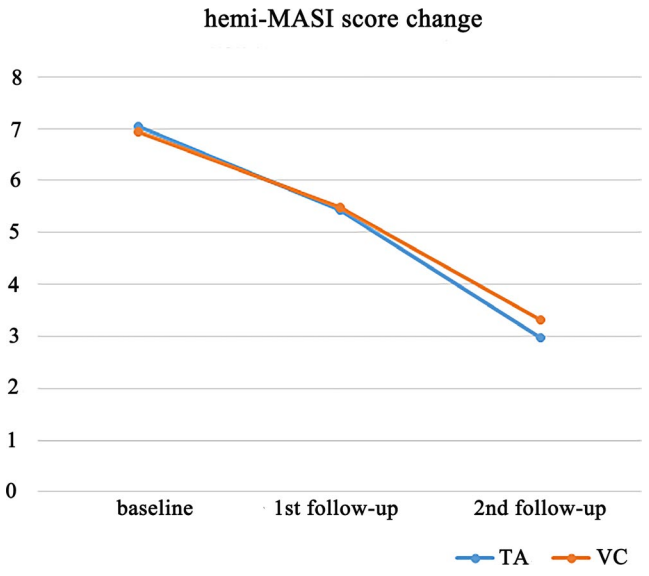

FIGURE 2 Variations in hemi-MASI during the treatment period

Myjet (Myjet, TavTech, Israel) is a device developed for facial rejuvenation and promoting transdermal absorption of topical drugs.[15] It consists of three parts: a handpiece, a control unit (on device body), and a footswitch. The basic principle of Myjet can be described as a mixture of water and oxygen forced into a channel, which accelerates the liquid through a nozzle at approximately 200 m/sec speed, delivering microdroplets of drug (diameter <3000 dalton) into the skin surface.[15,16]

Hemi-MASI was significantly decreased by transdermal injection of TA and VC after eight weeks, with no significant difference between the two drugs regarding the total reduction. Apparently, hemi-MASI in both sides decreased along with time, and the therapeutic effect of TA and VC occured after four weeks. Generally, the initial reduction of pigmentation in previous studies was usually observed after 1-2 months, but varied in different trials depending on the delivery method.[8,24,30] Our results are consistent with previous findings, and we concluded that Myjet-assisted TA or VC transdermal injection can assist pigment elimination. In this

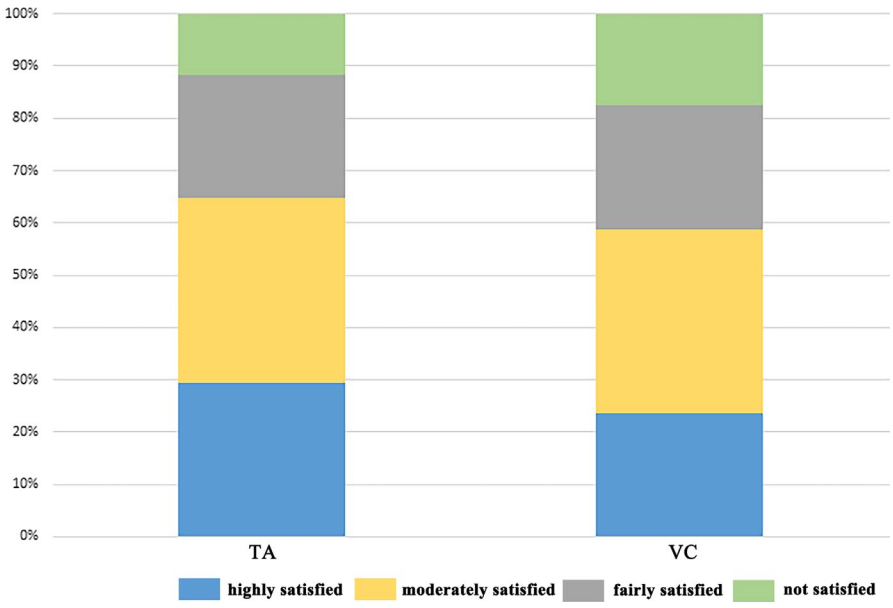

FIGURE 3 Patient satisfaction with tranexamic acid (TA) and vitamin C (VC) treatment

FIGURE 4 VISA image of a representative case showing clinical improvement by tranexamic acid (TA). A 47-year-old female (patient number 13 in Table 2) was treated with Myjet-assistant TA transdermal injection on the right side. The melasma on the right malar area showed gradual improvement (black arrows), and the brown spots in the lower panel showed a fading trend

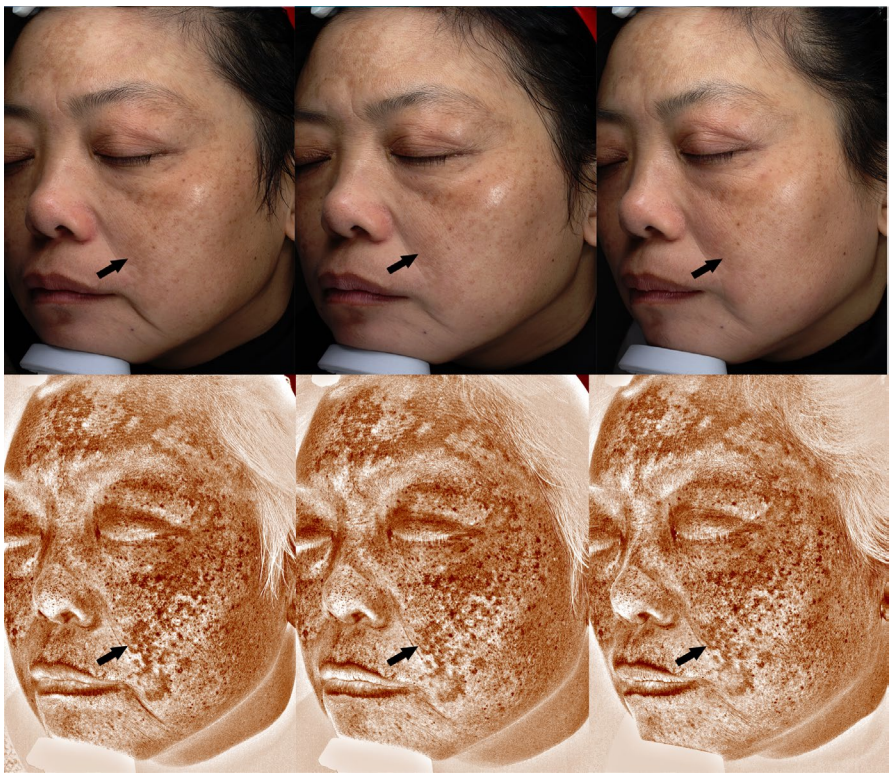

FIGURE 5 VISA image of a representative case showing clinical improvement by VC. A 47-year-old female (patient number 13 in Table 2) was treated with Myjet-assisted vitamin C transdermal injection on the left side. The melasma on the left malar area showed gradual improvement (black arrows)

split-face study, a statistically significant decrease in hemi-MASI was observed in the two study groups, indicating that weekly TA or VC transdermal injections may be a promising adjunctive treatment for melasma.

The total improvement rate in TA and VC groups was 76.4% and 64.7%, respectively. Two participants dropped out of this clinical trial, due to melasma aggravation after four weeks. We suspect that this may have been due to the powerful flux of microdroplet, which

stimulated the facial blood vessels. Three participants who received IPL treatments and one participant received picosecond laser in our study did not show clinical response, we doubt that the previous unsuitable laser/light parameters treatment stimulated melanocyte, and further study needs to be conducted. The adverse effects mainly included mild erythema and a stuffy feeling during the injection process, and they generally disappeared after treatment.

The advantages of our study include the split-face design, and the use of digital and VISA images for evaluation, since VISA has a higher light stability. Another advantage was the use of Myjet-assisted TA or VC in treating melasma, which may be a effective way for drug delivery.

There are several limitations in our study that should be noted. As observed in our study, the overall reduction in hemi-MASI was not different according to different drug. Due to the small sample size of the study group, there is a possibility of bias. Future studies with larger sample sizes may confirm our findings. Another limitation was the lack of blank control. Seasonal change is also a trigger factor when treating melasma, since sunlight increases during summer and might interfere with the treatment. Though participants in our study were instructed to apply an SPF 50 plus sunscreen during the treatment period, the other drawback of the study was the extended treatment period from winter to summer. The cure rate in the two groups was still limited, but may be a longer treatment duration is required to achieve greater improvement. Multiple factors may contribute to these differences including drug concentration, dosing and injection technique, severity, duration and type of melasma and so forth. Future studies are needed to resolve these issues.

5 | CONCLUSION

Our study revealed that Myjet-assisted TA or VC can be effective in treating melasma and may be more beneficial than systemic application in some patients with risk factors. However, further studies are required to address such point.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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