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The Importance of Publications in the Field of Aesthetic Medicine

Despite pandemic-induced economic downturns, the field of aesthetic medicine has demonstrated resilience and remarkable growth. Long-term prospects remain robust for major stakeholders and physicians advocating evidence-based medicine, aiming to disseminate pertinent, high-level knowledge on medical aesthetic practice and aging prevention.

In the scientific community, the 'publish or perish' adage remains pertinent. Successful publications bring attention to colleagues and sponsoring institutions, contributing to career advancement and securing ongoing research funding, thereby creating pressure for many individuals. Additionally, publications serve as avenues for networking with colleagues and securing speaking engagements at conferences-platforms to mentor the next generation of aesthetic practitioners.

The process of publishing an article, from conceptualization to manuscript riting, peer review, and eventual publication, is often underestimated. While the accomplishment of publication brings exhilaration, the journey itself can be a tedious and meticulous endeavour.

Publishing a case report, clinical trial, or observational study involves significant academic responsibility, demanding meticulous writing and precision. Creativity plays a role, whether in writing an original research topic, employing a novel methodological approach, or conveying new scientific observations.

For younger colleagues, beyond the personal gratification of sharing scientific discoveries, publishing research work offers a critical advantage-a bolstering of their curriculum vitae. This aspect is particularly crucial for residents-in-training aspiring to secure competitive post-graduate fellowship programs or positions within academic institutions.

In this March issue of JAPA, I wish to commend all contributors who have generously shared the outcomes of their research and hard work. Your contributions to the scientific community, especially in the field of aesthetic medicine, are immensely valued and appreciated.

Johannes F. Dayrit, FPDS, FDSP (PDS)
Editor

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CONTENT

ORIGINAL ARTICLE

An Update on the Current Practice in the Management of Melasma Patients by Dermatologists: A Cross-Sectional Online Survey in the Philippines

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Abstract: Melasma is a prevalent pigmentary disorder in the Philippines, with an estimated prevalence rate of 1.32%. The recurrent nature of melasma poses a significant therapeutic challenge among dermatologists in the country. This study aimed to evaluate the current practices in managing melasma among dermatologist who is a members of the Philippine Dermatological Society PDS). The cross-sectional online survey was conducted to evaluate the current practice in the management of melasma patients among 350 Filipino dermatologists. The survey was carried out from April 1, 2022, to September 30, 2022. The majority of respondents (71.4%) diagnosed melasma based solely on clinical examination. Among those who assessed melasma severity before treatment, the Melasma Area and Severity Index (MASI) score (50.7%) and the Melasma Severity Scale (25%) were the most commonly utilized methods. Regarding management, 49.1% of respondents opted for topical treatments alone, while 47.7% preferred combination therapies. Sunscreen was identified as the first line topical treatment (96.3%) followed by Kligman's cream, hydroquinone and tretinoin. For procedural methods, chemical peels ranked first (34.73%) as the preferred method. Approximately 62% of the respondents prescribed oral medications, with tranexamic acid (68.7%) being the most commonly prescribed, followed by glutathione (39.14%), vitamin C (37.39%), polypodium leucotomos (32.17%), and procyanidin (23.48%). Majority (56.9%) of the respondents considered shifting to alternative modalities after 4 to

6 months of treatment. Furthermore, 47.4% of the respondents preferred a maintenance duration exceeding one year. This study's findings delineate the current practices of 350 Filipino dermatologists in managing melasma patients. The outcomes will likely serve as a valuable reference for future melasma guidelines and treatment algorithms in the Philippines and neighboring countries.

Keywords: Melasma, Management of melasma, Philippines, Dermatologists

Introduction

Melasma is one of the most common pigmentary disorders with an incidence as high as 30% in Asian women of childbearing age [1]. It presents clinically as brown macules or patches on the centrofacial, malar or mandibular region of the face, but more commonly presents with an overlap of the aforementioned clinical patterns [2]. Several risk factors that contribute to its pathogenesis include Fitzpatrick skin types III and IV, genetic predisposition, ultraviolet light exposure, pregnancy, and exogenous hormones while less commonly reported are thyroid disorders, phototoxic medications, and cosmetics [3]. Although considered as a benign condition, it certainly has an impact on the patients' quality of life, as affected individuals have low self-esteem, decreased social interaction and outdoor activities [4].

The exact prevalence of melasma worldwide is unknown, despite multiple studies conducted on the epidemiology of melasma in various countries. According to Khoza et al [5], melasma is most prevalent among Fitzpatrick skin phototypes III to V and patients of Hispanic, Latin American, Asian, Middle Eastern, and African descent.

The Philippine Dermatological Society (PDS) is a growing group of dermatologists in the Philippines with a 70-year history. Each of its members has undergone three years of training at its accredited institutions, encompassing both medical and cosmetic fields. In 2011, PDS developed its Health Information System (PDS-HIS), allowing comprehensive reporting of all related cases, both old and new, from its eleven accredited training institutions. Among the 809, 851 recorded dermatology cases from 2011 to 2022 [6], a total of 10,683 cases were reported as melasma (1.32%), with 9,350 identified as new cases (1.15%). Additionally, the study conducted by Gener-Pangilinan et al [7] reported the prevalence of melasma among Filipino patients seen at six government hospitals and private clinics, and reported a prevalence rate of 1.26%.

Topical hydroquinone 4% remains the gold standard of treatment [8], but there are other alternatives currently available, ranging from topical and oral medications to in-office procedures such as chemical peels and energy-based devices. In 2005, a local study investigated the various treatment modalities employed by practicing Filipino dermatologists and found that the top three topical depigmenting agents being used were tretinoin, hydroquinone and combination therapy. Among in-office procedures, microdermabrasion was preferred over laser therapy while vitamin C and glutathione emerged as the most commonly prescribed oral maintenance agents [9].

Unfortunately, melasma often presents with frequent recurrences, posing a therapeutic challenge for dermatologists. Therefore, an up-to-date investigation into the treatment strategies for melasma involving a larger cohort of local dermatologists is desirable. Hence, this study aimed to determine the current practices in managing melasma in the Philippines among dermatologists and dermatology resident physicians undergoing training at various PDS accredited institutions. Additionally, considering the absence of a local guideline for melasma management, this study can serve as a crucial resource for developing melasma care guidelines and treatment algorithms in the Philippines.

Methodology

Study Design and Study Procedure

This is a descriptive, cross-sectional study conducted using an online survey form. The questions in the survey were discussed and approved by a panel of 11 expert dermatologists from the Pigmentary Disorders Interest Group of the PDS. The study was reviewed and approved by the Institutional Review Board of San Juan De Dios Educational Foundation Inc. The finalized survey was disseminated via Google Forms, with a link distributed to eligible respondents (refer to inclusion criteria for selection) through emails to their respective affiliated institutions of the expert members. The survey was conducted for 6 months, from April 1, 2022 to September 30, 2022. Subsequently, the collected results were collated and sent to a statistician for analysis. The respondents were recruited based on inclusion and exclusion criteria detailed below.

Inclusion criteria:

1. Dermatologists who completed a 3-year residency training program in PDS accredited training institutions:
    1.1. Diplomates: Graduates of a 3-year dermatology training program from an accredited PDS institution who passed the Philippine Board of Dermatology.
    1.2. Fellows: Individuals who meet the qualifications of a diplomate and have completed two consecutive years of private or government practice.

2. Dermatology residents/trainees currently undergoing training in PDS institutions (from first to third year levels).

Exclusion criteria:

1. PDS board-certified dermatologists practicing full-time abroad.

Sampling and Sample Size

Quota sampling was used, and the sample size was determined using Slovin's formula [10]. Consent was obtained from eligible respondents and the recruitment was conducted until the required sample size was achieved. As of December 2022, the PDS consisted of 1,448 dermatologists, comprised of 1,279 board-certified dermatologists and 169 residents. With a 95% confidence level, 5% margin of error, and an estimated population proportion of 80%, the calculated minimum sample size required was 207 for board-certified dermatologists and 101 for residents.

Tool

The survey is comprised of 34 questions, featuring a combination of multiple-choice (21 questions) and free-text (13 questions) formats. Multiple-choice questions include pre-determined answer options or require ranking of listed items. The scope of the survey encompasses three main areas: respondent profile (eight questions), melasma diagnosis (four questions) and melasma management practices (22 questions). The English language was used in the survey.

Statistical Analysis

Statistical Package for the Social Sciences (SPSS) version 28 was used to analyze the data. Frequency, percentage, and mean were used to demonstrate the demographic profile data of the respondents and to describe the data gathered from the online survey.

Results

Demographic Profile of the Respondents

A total of 350 respondents were included in the study. Female comprised the majority (n=314, 89.7%) of respondents compared to male (n=36, 10.3%). The age of respondents ranged from 21 to 80 years old, with the majority falling in the 31 to

40-year age range (n=106, 30.3%). Respondents consisted of PDS fellows (n=189, 54%), diplomates (n=58,16.6%) and dermatology residents-in-training from first to third year (n=103, 29.5%). The majority of PDS fellows and diplomates have been practicing for more than 20 years (n=101, 40.9%). Predominantly, most of the respondents practiced or trained in the National Capital Region of the Philippines (n=226, 64.6%). The most common type of practice was a combination of hospital and private practice (n=148, 42.3%), with a majority (n=208, 59.4%) handling both general dermatology and aesthetic cases. Meanwhile, aesthetic-focused practices accounted for only 2.9% (n=10) of respondents **(Table 1)**.

Table 1. Demographic profile of the respondents.

Demographic profile	n	%
Age (years)		
21- 30	73	20.9
31-40	106	30.3
41 -50	58	16.6
51 - 60	72	20.6
61 - 70	35	10
71 - 80	6	1.7
Gender		
Male	36	10.3
Female	314	89.7
PDS Consultant or Resident		
1st year resident	30	8.6
2nd year resident	23	6.6
3rd year resident	50	14.3
Diplomate	58	16.6
Fellow	189	54
Years of Practicing as a Dermatologist		
1 to 5	54	21.9
6 to 9	28	11.3
10 to 20	64	25.9
>20	101	40.9
Region Currently Practicing/Training		
Region I-II	28	8
Region III	37	10.6
Region IV	47	13.4
Region V	11	3.1
Region VI	3	0.9
Region VII	7	2
Region VIII	0	0
Region IX	3	0.9
Region X	3	0.9

Region XI	9	2.6
Region XII	5	1.4
Region XIII	3	0.9
NCR	226	64.6
MIMAROPA	1	0.3
CAR	3	0.9
ARMM	1	0.3
Type of Dermatological Practice		
Hospital based practice	109	31.1
Private practice	93	26.6
Both hospital and private practice	148	42.3
Frequently Seen Cases		
General dermatology/pathologic cases	132	37.7
Predominantly aesthetic cases	10	2.9
Both general dermatology/pathologic and aesthetic cases	208	59.4

NCR – National Capital Region; MIMAROPA – Mindoro Occidental, Mindoro Oriental, Marinduque, Romblon, Palawan; CAR – Cordillera Administrative Region; ARMM – Autonomous Region in Muslim Mindanao

Diagnosis of Melasma

Results revealed that majority of the respondents diagnose melasma using clinical examination only (n=250, 71.4%). A smaller percentage combined clinical examination with other methods such as dermoscopy (19.4%), Wood's lamp examination (15.4%) and skin biopsy (2%) as shown in **Figure 1**. Prior to initiating treatment, the majority of respondents (n=209, 59.7%) did not measure melasma severity. Among those who assessed melasma severity before treatment (n=141, 40.3%), the Melasma Area and Severity Index (MASI) score (n=69, 50.7%) and the Melasma Severity Scale (n=34, 25%) were the two most commonly used methods. More than half of the respondents (n=209, 59.7%) determined the melasma subtype prior to treatments.

Management of Melasma

First-line treatment option for melasma

The most common first-line treatment option for melasma among respondents was topical treatment alone (n=172, 49.1%) followed by combination treatment (n=167, 47.7%). Among those opting for combination treatments, topical medications were often combined with various procedures. These included chemical peels (n=58, 34.73%), other topical medications (n=34, 20.36%), laser therapy (n=19, 11.38%), a combination of chemical peels and laser (n=18, 10.78%), oral medications (n=15, 8.98%), other procedures such as microneedling, micro-dermabrasion, platelet rich plasma (PRP), or exosomes (n=9, 5.39%), combinations of oral medications and chemical peels (n=6, 3.59%), oral medications with chemical peels and laser treatments (n=2.99%), and oral medications with laser treatments (n=3, 1.8%). Sunscreen emerged as the most preferred topical treatment, followed by various formulations of the modified Kligman's cream, hydroquinone and tretinoin **(Figure 2)**. Of the 337 (96.3%) respondents who chose sunscreen as their preferred topical treatment for melasma, 97.33% (n=328) chose an SPF level between 30 to 50. Meanwhile SPF >50

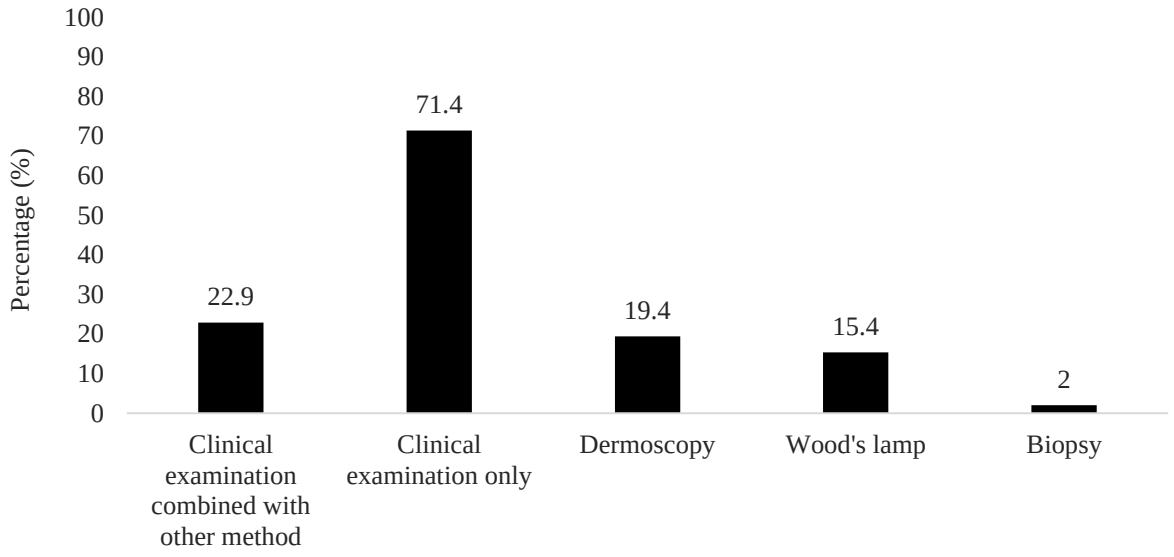

Figure 1. Methods for diagnosis of melasma.

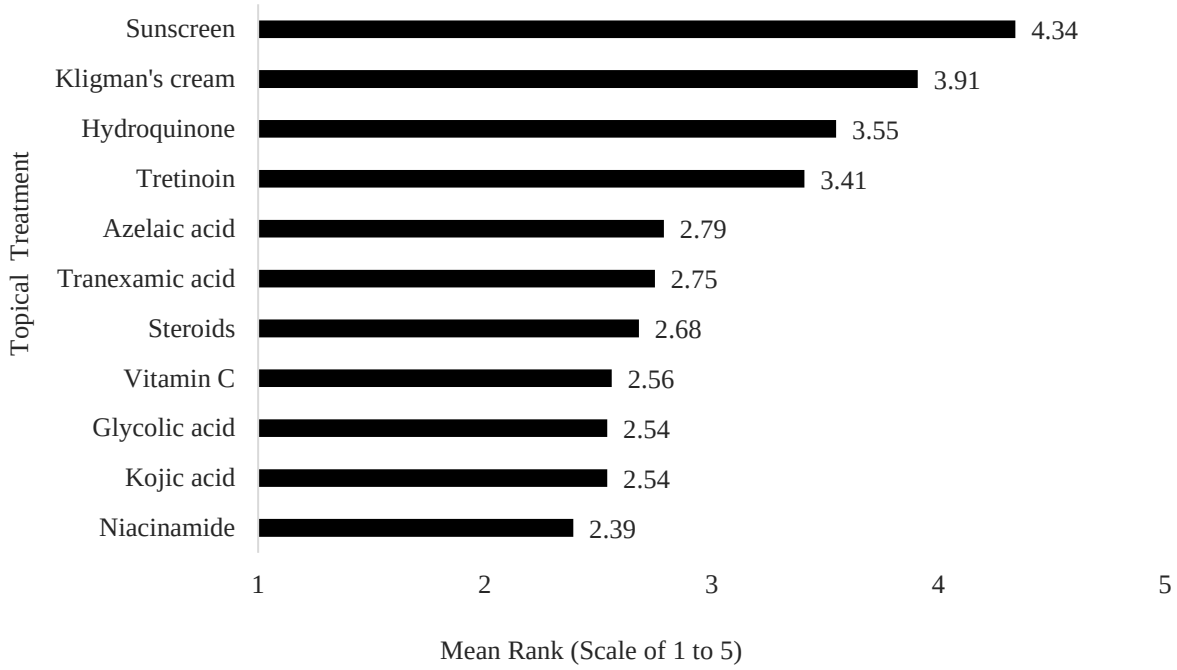

Figure 2 Topical treatments options for melasma.

is preferred by a few respondents (n=8, 2.37%) and only 0.38% (n=1) prescribing sunscreen with an SPF <30.

Procedural treatment options for melasma

Of the available procedural methods used for the management of melasma, chemical peel ranked the highest, followed by laser treatment. The least preferred procedural methods are iontophoresis **(Figure 3)**.

Oral medication treatment options for melasma

Oral medications were prescribed by 62% (n=217) of the respondents, with tranexamic acid (TA) (n=79, 68.7%), ranking first, followed by glutathione (n=45, 39.14%), vitamin C (n=43,

37.39%), polypodium leucotomos (n=37, 32.17%), and procyanidin (n=27,23.48%) **(Figure 4)**.

Dosage of prescribed oral medications for melasma

Tranexamic acid, being the most prescribed oral medication, was given by 66.09% (n=76) of the respondents at a preferred total daily dose of 500 mg (single dose or 250 mg 2 times per day). Glutathione with variable dosing from 200 mg to 1,500 mg, was mostly given at 500 mg per day (n=33, 84.6%). Polypodium leucotomos was given by the majority of respondents at 480 mg daily (n=22, 59.46%). Meanwhile, Vitamin C was given at doses ranging from 500 mg to 1,000 mg per day (n=41, 95.35%) and procyanidin was prescribed with 48 mg as the preferred total daily dose (n=24, 20.87%).

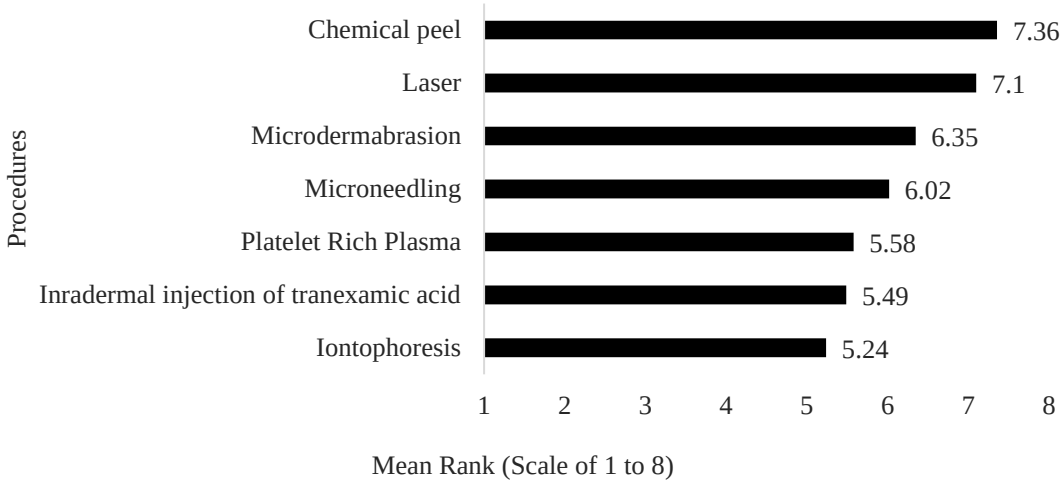

Figure 3 Procedural treatment options for melasma.

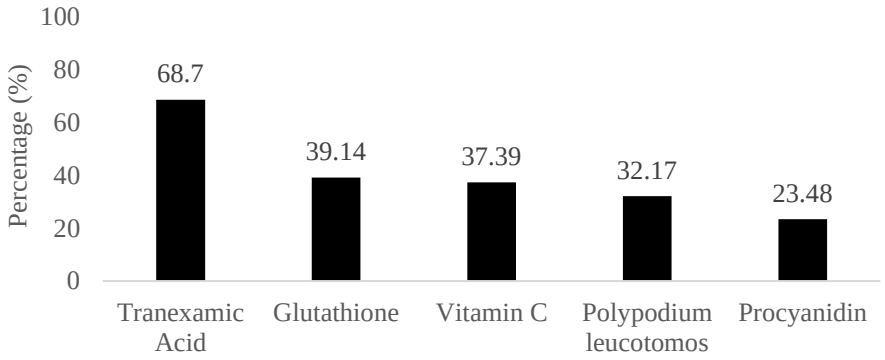

Figure 4 Oral medication treatment options for melasma.

Duration of intake of prescribed oral medications for melasma

Tranexamic acid was given at a range of 1 to 12 months, with the majority of respondents (n=44, 59.46%) prescribing it for 3 months. Procyanidin was prescribed for 3 months by the majority of the respondents (n=9, 31.03%). Polypodium leucotomos (n=14, 38.89%), glutathione (n=15, 32.61%) and ascorbic acid (n=21, 26.09%) were

given indefinitely by the majority of the respondents.

Shifting to another treatment option for melasma

Majority of the respondents in this survey considered shifting to another alternative modality after 4 to 6 months (n=199, 56.9%) but 33.4% (n=117) preferred an earlier period of 1 to 3 months. The most common reason for shifting was non-improvement, followed by worsening of the condition, presence of side effects from the medication and recurrence of melasma. Cost of medication was the least common cause.

The frequency of follow-up for melasma

Monthly follow-up was preferred by most of the respondents (n=241, 68.9%), followed by less than a month (n=61, 17.4%), every 2 months (n=35, 10%) and more than 2 months (n=13, 3.7%).

Maintenance therapy prescribed for melasma

For maintenance therapy of melasma, sunscreen was the most prescribed, followed by tretinoin, modified Kligman's cream and topical vitamin C, respectively. The least prescribed were steroids and kojic acid **(Figure 5)**. A maintenance therapy duration of more than one year is preferred by 47.4% (n=166) of the respondents, followed by 3 to 6 months (n=93, 26.6%) and 6 to 12 months (n=77, 22%). Only 4% (n=14) of the respondents maintained their patients on medications for less than 3 months.

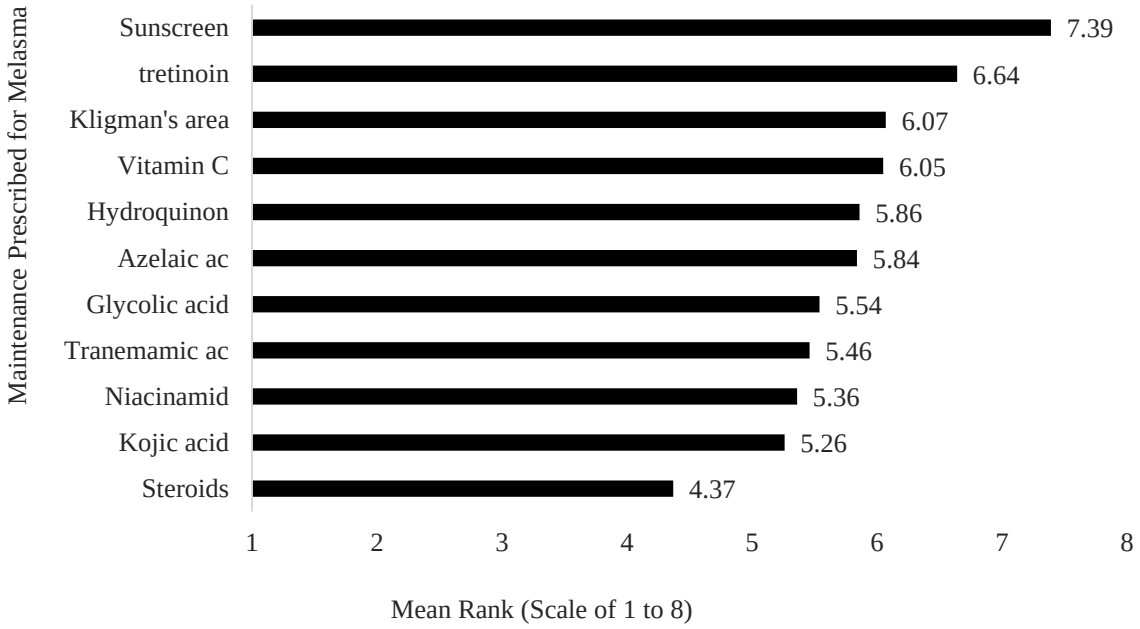

Figure 5 Maintenance therapy prescribed for melasma patients

Confidence in managing melasma patients

Management of melasma cases is included in the basic training of dermatologists. Attending workshops or seminars helps affirm their knowledge and broaden their approach in handling melasma patients. In this study, 157 (44.9%) respondents engaged in seminars/work-shops related to melasma, while 193 (55.1%) respondents did not. Regarding confidence in managing melasma, the majority of respondents rated their level as fairly confident (n=177, 50.6%). Only a small percentage expressed complete confidence (n=22, 6.3%), and very few claimed to have no confidence at all (n=6,1.7%).

Discussion

Numerous studies have explored the prevalence of melasma and its impact on patients' quality of life. Furthermore, the clinical epidemiologic features and treatment options for melasma have been well-researched. However, there is still a paucity of studies regarding melasma management in the Philippines, highlighting the need to identify how dermatologists in the country manage this condition.

There are various methods available to diagnose melasma, with clinical examination of skin pigmentation being the most commonly used approach. The majority of respondents in this study relied solely on clinical presentation for diagnosis, while only a third combined clinical examination with other methods such as Wood's Lamp and dermoscopy. Only a few of the respondents performed a skin biopsy, which was primarily advocated in cases where there was uncertainty in the diagnosis. Wood's Lamp illumination helps distinguish between epidermal and dermal melasma. However, in individuals with darker skin and mixed types of melasma, Wood's Lamp examination might yield inconclusive results [11,12]. Additionally, the introduction of dermoscopy has aided in distinguishing melasma from other hyperpigmentary disorders [13-15], although it necessitates familiarity with the equipment and accurate interpretation of the structures. These diagnostic techniques, excluding more sophisticated methods like spectrophotometry and VISIA imaging, were mentioned in the 2021 version of the Consensus on the Diagnosis and Treatment of Melasma in China [1]. In the therapeutic ladder recommended by Sarkar et al [16], clinical assessment is conducted along with Wood's Lamp examination whenever feasible for the diagnosis of melasma.

Once the diagnosis of melasma is confirmed, it is essential to conduct objective assessments not only by capturing before and after photographs but also by employing a severity scoring system that one is proficient with. Various scales, such as the Melasma Area Severity Index (MASI), modified Melasma Area Severity Index (mMASI), Melasma Severity Score (MSS), and Melasma Severity Index (MSI), have been developed and have proven to be helpful in assessing improvements in melasma [17,18]. Preferences regarding which assessment to use vary among practitioners. While MSS and MSI are less popular than MASI and mMASI, they are considered more practical and easier to use in daily clinical practice [18]. Despite being taught during residency, the utilization of these measurements is not mandatory for every clinician or dermatologist treating melasma. This is evident in this survey, where the majority of respondents do not use scales or indices to measure melasma severity during patient treatment. Among the respondents who do use severity scales, MASI and MSS emerged as the two most preferred assessment scoring systems.

Melasma is a complex hyperpigmentary disorder, considering its multifactorial nature and evolving pathology [19]. As such, there is still no optimal therapeutic regimen for melasma sufferers. The response to treatment varies among individuals, which significantly impacts clinicians' confidence in managing melasma cases. In the context of the Philippine setting, despite years of training and clinical practice as dermatologists, only 6.3% reported complete confidence in managing melasma cases, with the majority (50.6%) indicating a fair level of confidence. Meanwhile, a study conducted by Ma et al [20] found that only 2% of respondents from the British Association of Dermatologists reported having high confidence levels in managing melasma and post-inflammatory hyperpigmentation cases.

This study revealed that the majority of respondents adhere to international guidelines [1] in managing melasma. Topical treatment plays a significant role in their management strategies, either used alone or in conjunction with procedural methods and oral medications. These practices align with findings from an earlier study on melasma treatment strategies in the country

[9]. Combination treatments usually preferred and can be utilized to optimize management, particularly in challenging cases as monotherapy may not offer significant benefits to patients [3]. Topical lightening agents such as hydroquinone, retinoids, and a combination of both, are considered a first-line management approach for melasma [3,16,21], often used in conjunction with topical corticosteroids. Hydroquinone, recognized as the gold standard for treating melasma, and tretinoin, a known photoaging agent, are widely used either alone or in combination with fluocinolone as triple combination creams (TCC) or dexamethasone as Kligman's cream. Notably, one of the most successful combination for topical treatment consists of 4% hydroquinone, 0.05% tretinoin, and 0.01% fluocinolone acetonide. Meanwhile, variations of the Kligman's formula have shown to be the most clinically effective initial therapy for patients with melasma [3,21]. Additionally, other commonly used topical agents include azelaic acid, kojic acid, ascorbic acid, arbutin, licorice extract, and soy [3,16] which are utilized to mitigate potential side effects associated with hydroquinone and tretinoin. Sunscreen usage is considered mandatory, with a preferred SPF range of 30 to 50.

In-office procedures for melasma management encompass chemical peels, laser treatments, and light therapies. Chemical peels such as glycolic acid, trichloroacetic acid (TCA), Jessner's solution, tretinoin, or their combinations are typically recommended as second-line therapy [16]. Meanwhile, laser and light-based treatment options, which have been increasingly gaining popularity for managing melasma, are considered as third-line therapy in the algorithm proposed by Sarkar et al [16] and are advocated only for the inactive stage of melasma according to the recent consensus on melasma in China [1]. The therapeutic ladder for melasma proposed by Trivedi et al [22] also suggest laser and light-based treatments as third-line therapy, to be used in combination with first-line therapies (after maximizing topical medications and chemical peels) for management of melasma cases. Laser and light therapy for melasma can be classified into five categories: intense pulsed light (IPL), Q-switched lasers, picosecond lasers, nonablative fractionated resurfacing lasers, and ablative fractionated resurfacing lasers. Among these treatments, non-ablative fractional lasers demonstrate the most beneficial outcomes, as it is capable to treat a wider range of skin types, including Fitzpatrick skin types III-VI [22]. In the present study, respondents preferred employing chemical peels and lasers in conjunction with topical treatments for managing melasma. Additionally, other methods used for managing melasma included microdermabrasion, micro-needling, PRP, intradermal injection of TA, and iontophoresis.

Among the oral treatment options for melasma, TA, glycyrrhizin, Vitamin C, glutathione, procyanidin, polypodium leucotomos, pycnogenol, carotenoid and melatonin have been mentioned in reviews and consensus recommendations [1,16]. Oral TA is the preferred choice of oral treatment for melasma among the respondents in this study, with the majority prescribing it at a dose of 500 mg daily for 3 months. Tranexamic acid was the most studied oral medications for melasma, showing considerably good results [1,16,23]. It can be used alone [16] or together with topical agents [1,16]. The recommended dose is 250-500 mg once or twice a day for three to 3 to 6 months [1]. The other oral medications, though showing promising results, require further evidence to be recommended as monotherapy for melasma [1,16,24]. However, inclusion in the management as an adjunct may offer good treatment outcomes due to their anti-inflammatory and antioxidant effects [23].

The primary goals in treating melasma are to lighten or completely remove hyperpigmentation and prevent its recurrence [1]. Given its unpredictable nature and resistance to treatment, managing melasma should extend beyond resolving hyperpigmentation. The response to treatment can span 3 to 12 months or longer [25], thereby making the duration of treatment pivotal for successful outcomes [1,16]. At present, there

are no set rule on the duration of melasma treatment [1,16,22]. However, it is crucial that once the desired lightening is achieved, a maintenance regimen is implemented. This includes controlling risk factors, using safe topical agents, and intermittently incorporating procedural treatments [22]. In this study, majority of the respondents typically treat melasma for up to 6 months, conducting monthly follow-ups, before considering alternative management, usually due to a lack of improvement. Due to recurrence tendency of melasma, maintenance treatment was implemented, for periods ranging from 3 months to over a year. These involve the use of topical sunscreen, tretinoin, Kligman's cream, or vitamin C serum.

Conclusion

This study examined the current practices of 350 Filipino dermatologists in the management of melasma patients. In this study, sunscreen was the most commonly prescribed first line treatment and maintenance medication for melasma, while a significant number of respondents continue to recommend various formulations of the modified Kligman formula, tretinoin, and hydroquinone combinations. This study found that only a few of the respondents expressed complete confidence in managing melasma, while half of the respondents reported being fairly confident. Almost half of the respondents relied solely on topical treatments, while the other half opted for combination therapies involving chemical peels, lasers, and oral medications like TA, pycnogenol, glutathione, and Polypodium Leucotomos. Moreover, the majority of respondents considered shifting to alternative modalities after 4 to 6 months of treatment. Nearly half of the respondents preferred a maintenance therapy duration of over one year. The findings of this study can potentially serve as a reference point for updating melasma guidelines and treatment algorithms in the Philippines.

Limitations of Study

This study is not without limitations. One of its limitations was the failure to inquire about complications encountered from melasma treatments and how they were managed.

Conflict of Interest

There is no potential conflict of interest.

Funding Source

There is no funding involved in this study.

References

1. Gao TW, Gu H, He L, Lei TC, Lil M, Li TN, et al. Consensus on the Diagnosis and Treatment of Melasma in China (2021 version). International Journal of Dermatology and Venereology. 2021;4(3): 133-139.
2. Rodrigues M, Pandya AG. Melasma: clinical diagnosis and management options. Australasian Journal of Dermatology. 2015;56(3):151-163.
3. Sheth VM, Pandya AG. Melasma: A comprehensive update. Journal of the American Academy of Dermatology. 2011;65(4):689-697.
4. Jiang J, Akinseye O, Tovar-Garza A, Pandya AG. The effect of melasma on self- esteem: a pilot study. International Journal of Women's Dermatology. 2018; 4:38-42.
5. Khoza N, Dlova N, Mosam A. Epidemiology and Global Distribution of Melasma. In Sarkar R (ed), Melasma: A Monograph. Jaypee Brothers Medical Publishers, 1-3. 2015.
6. Philippine Dermatological Society Health Information Systems. Philippine Dermatological Society. C2011, February 9, 2023. [cited February 2023]. Available by request from: pdshis@outlook.

7. Gener-Pangilinan LA, Handog EB, Gabriel MT, Carpio BD, Lavadia MA, Loginus W, et al. Prevalence, epidemiology, and clinical characteristics of melasma in Philippine dermatology patients: a multicenter, cross sectional study. Journal of the Philippine Dermatological Society. 2019;28(1): 15-23.
8. Rodrigues M, Pandya AG. Hypermela-nosis. In: Kang S, Amagai M, Bruckner AL, Enk AH, Margolis DJ, McMichael AJ, et al. (eds). Fitzpatrick's Dermatology 9th Edition, 1379-1381. New York:McGraw Hill Education; 2019.
9. Pearl, FAC, Flordeliz ACM. A descriptive study on the treatment strategies for melasma used in the Philippines. Journal of the Philippine Dermatological Society. 2011; 20(2):42-49.
10. Glen S. "Slovin's Formula: What is it and When do I use it?". StatisticsHowTo.com: Elementary Statistics for the rest of us!, Aug 10, 2023. [cited Aug 2023] Accessed from:https://www.statisticshowto.com/probability-and-statistics/how-to-use-slovins-formula/.
11. Sehgal VN, Verma P, Srivastava G, Aggarwal AK, Verma S. Melasma: treatment strategy. Journal of Cosmetic and Laser Therapy. 2011;13(6):265-279.
12. Dyer JM, Foy VM. Revealing the unseen: a review of Wood's lamp in dermatology. The Journal of Clinical and Aesthetic Dermatology. 2022;15(6):25-30.
13. Bhattar PA, Zawar VP, Godse KV, Patil SP, Nadkarni NJ, Gautam MM. Exogenous Ochronosis. Indian Journal of Dermatology. 2015; 60:537–543.
14. Khunger N, Kandhari R. Dermoscopic criteria for differentiating exogenous ochronosis from melasma. Indian Journal of Dermatology, Venereology and Leprology. 2013; 79:819-821.
15. Sonthalia S, Jha AK, Langar S. Dermoscopy of melasma. Indian Derma-tology Online Journal. 2017;8(6): 525-526.
16. Sarkar R, Gokhale N, Godse K, Ailawadi P, Arya L, Sarma N, et al. Medical management of melasma: A review with consensus recommendations by Indian pigmentary expert group. Indian Journal of Dermatology. 2017;62(6): 558-577.
17. Majid I, Haq I, Imran S, Keen A, Aziz K, Arif T. Proposing Melasma Severity Index: A New, More Practical, Office-based Scoring System for Assessing the Severity of Melasma. Indian Journal of Dermatology. 2016;61(1):39-44.
18. Heidemeyer K, Cazzaniga S, Feldmeyer L, Imstepf V, Adatto M, Lehmann M, et al. Skin hyperpigmentation index in melasma: A complementary method to classic scoring systems. Journal of Cosmetic Dermatology. 2023;22(12):3405 -3412.
19. Rajanala S, Maymone M, Vashi NA. Melasma pathogenesis: a review of the latest research, pathological findings, and investigational therapies. Dermatology Online Journal. 2019;25(10): 13030/qt47b7r28c.
20. Ma Y, Millette D, Nalluri R, Yoo J. UK-based dermatologist online survey on the current practice and training in the management of melasma and postinflammatory hyperpigmentation. Clinical and Experimental Dermatology. 2020;45(4):483-484.
21. Shankar K, Godse K, Aurangabadkar S, Lahiri K, Mysore V, Ganjoo A, et al. Evidence-Based Treatment for Melasma: Expert Opinion and a Review. Dermatology and Therapy. 2014;4:165-186.
22. Trivedi MK, Yang FC, Cho BK. A review of laser and light therapy in melasma. International Journal of Women's Dermatology. 2017;3(1):11-20.
23. Zhou LL, Baibergenova A. Melasma: systematic review of the systemic treatments. International Journal of Dermatology. 2017;56(9), 902-908.
24. Cassiano DP, Espósito AC, da Silva CN, Lima PB, Dias JA, Hassun K, et al. Update

on Melasma—part II: treatment. Dermatology and Therapy. 2022;12(9): 1989-2012.
25. American Academy of Dermatology. Melasma: diagnosis and treatment, August 30, 2023. [cited August 2023] Accessed from: https://www.aad.org/public/diseases/a-z/melasma-treatment.

ORIGINAL ARTICLE

Tolerance and Efficacy of a Combined Prebiotic and Postbiotic-Based Moisturizer as a Complementary Treatment in Patients with Predominance Phototype IV Diagnosed with Mild to Moderate Acne

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Abstract: Acne is a common skin disorder that has the potential to cause physical scarring and significantly impact the quality of life (QOL). This observational study aims to evaluate the efficacy and tolerance of combined prebiotic and postbiotic- based moisturizer, either alone or as a complement to topical and systemic treatments, in patients with mild to moderate acne. Patients aged 14 years and above, with mild to moderate acne based on a validated Global Evaluation Acne (GEA) score of I to III, received Effaclar Duo (+) for a duration of 60 days. The evaluation of its efficacy, targeting both types of lesions (20.5% retentional, 28.3% inflammatory, 51.2% mixed), and preventing colored marks, was assessed using GEA score, observed seborrhea level, skin-colored marks, Cardiff Acne Disability Index (CADI) scores, and clinical examinations at day 0 (D0) and day 60 (D60). Demographic data, acne onset duration, and skin phototype of patients were collected at D0. Additionally, both patients and assessing dermatologists completed self-administered questionnaires to assess tolerance and acceptability at D60. In this study, a total of 268 patients from the local cohort, with a mean age of 24.4 ±7.8 years, GEA scores ranging from I to III, and 51% of the patients with skin phototype IV, were recruited. The results showed a statistically significant ($p < 0.0001$) improvement of the GEA Grade in 48% of the patients at D60. A significant reduction ($p < 0.0001$) of up to 47% in seborrhea level was observed at D60. Significant improvement in erythematous marks ($p < 0.0001$) and pigmentary marks ($p < 0.0001$), seen in 44% and 42% of patients, respectively. Furthermore, there was a significant ($p < 0.0001$) improvement in the QOL among patients, with 27.5% reduction in CADI score. In conclusion, Effaclar Duo (+), which contains Aqua Posae Filiformis, was proven to reduce acne severity, skin post-inflammatory erythema and pigmentation, and skin seborrhea, thereby enhancing the QOL for local patients with mild to moderate acne.

Keywords: Acne, Effaclar duo (+), Prebiotic moisturizer

Introduction

Acne is a common, chronic inflammatory skin disorder of the pilosebaceous unit. Its established pathophysiology involves abnormal-ities such as hyperseborrhea, follicular keratin-ization, proliferation of *Propionibacterium acnes* or *Cutibacterium acnes*, and inflammation. Clinically, acne is characterized by seborrhea, noninflammatory, and inflammatory lesions. Alterations in the sebaceous lipid profile, particularly during puberty, stress, irritation, cosmetic use, and potential dietary factors, trigger skin inflammation and the formation of different types of acne lesions [1]. Genetic factors significantly influence the proportion of branched fatty acids found in sebum, with heritability estimates ranging from 50% to 90%.

The pathogenesis of acne also involves the interaction of several host factors, including the stimulation of sebaceous glands by circulating androgens and dysbiosis of the pilosebaceous follicle microbiome. Dysbiosis is a process leading to a disturbed skin barrier and disequ-ilibrium of the cutaneous microbiome [2]. The pro-inflammatory activity of the cutaneous microbiome could result in the proliferation of *P. acnes* strains [3].

Effaclar Duo (+) moisturizing cream contains a unique thermal fragmented bacterial extract (postbiotic) resulting from the prebiotic Aqua Posae Filiformis (APF). The prebiotic APF is derived from the boosted probiotic *Vitreoscilla Filiformis* bacterium in a medium enriched with thermal spring water [4,5]. Aqua Posae Filiformis helps rebalance the skin microbiome and strengthen the skin barrier, ultimately improving acne-prone skin. The cutaneous microbiota on the surface of acne-prone skin is characterized by the overexpression of *Staphylococcus*, which in excess triggers inflammatory cascades, resulting in inflamed skin. Aqua Posae Filiformis's action on the skin microbiome favors the growth of commensal bacteria, reduces the abundance of *Staphylococcus*, and increases the synthesis of antimicrobial peptides (AMP) in the skin. An increased skin innate system, AMP, strengthens the skin barrier through inflammatory regulation.

Acne is commonly associated with seborrhea, with hormonally responsive sebaceous glands abundant on the face, neck, chest, upper back, and upper arm areas. Inflammatory acne presents with erythematous lesions, such as papules, pustules, or nodules. Resolving acne lesions may manifest with post-inflammatory hyperpigmentation, more common in individuals with darker skin (phototypes IV to VI). Management of acne aims to resolve active lesions and prevent new ones, requiring at least 2 to 3 months of treatment compliance for complete resolution. An effective treatment response should involve a noticeable reduction in active lesions rather than complete clearance, along with a reduction in seborrhea and post-inflammatory signs (erythema, pigmentation).

Effaclar Duo (+) is prescribed as part of the treatment protocol in inflammatory acne and can be used alone in retentional non-inflammatory acne. It also contains glycerin (humectant moisturizer). To date, there is a lack of clinical data on the efficacy and tolerability of Effaclar Duo (+) in our local cohort. This study aims to evaluate the tolerance and efficacy of Effaclar Duo (+) as a complement to topical treatment, associated with systemic treatment (except isotretinoin), or used alone in patients with mild to moderate acne in a Malaysian cohort.

Methodology

Study Design and Patients

This observational, prospective cross-sectional, open label study analysed 268 patients **(Figure 1)**. The study was conducted with institutional ethical approval (REC12/2021;MR/1051) from Univer-siti Teknologi MARA (UiTM). The patients were recruited using universal sampling. Informed consent was obtained from the patient or their parent/guardian if the patient is under 18 years old before the study commenced. The inclusion criteria were individuals aged 14 years or above,

diagnosed with mild to moderate acne based on validated Global Evaluation Acne (GEA) scoring system **(Table 1)**, ranged from 1 to 3 (hardly any lesions to moderate), prescribed with topical or systemic acne treatment, or both, or otherwise prescribed with Effaclar Duo (+) alone. The appropriate existing treatments before patient study enrolment will be continued with the addition of Effaclar Duo (+). Acne-treatment-naive patients at study enrolment will be given either Effaclar Duo (+) alone or with other appropriate treatment according to standard practice. Patients undergoing isotretinoin treatment and those treated with isotretinoin in the past three months were excluded from the study.

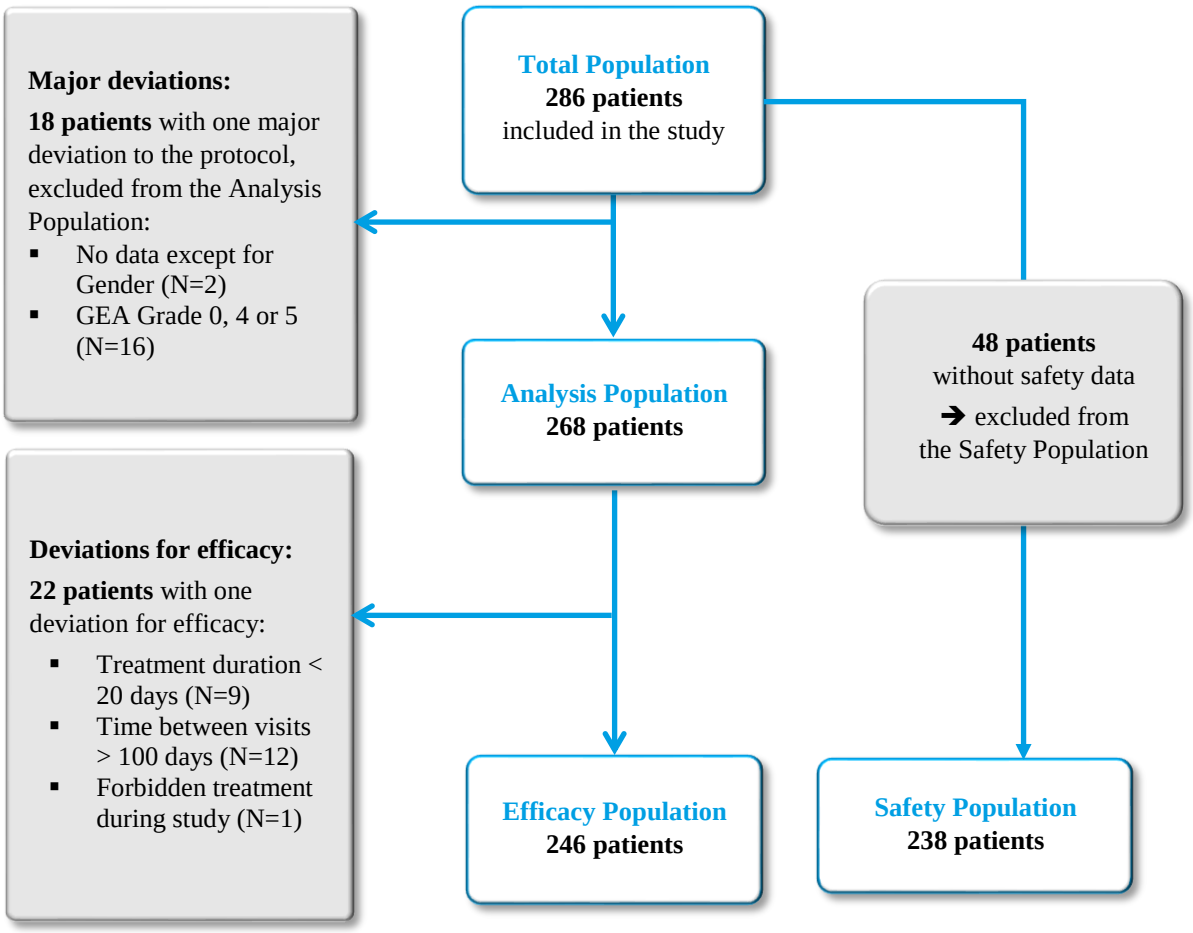

Figure 1 Number of patients and deviations.

Study Protocol

All patients enrol in the study were given a combined prebiotic and postbiotic-based moisturizer (CPPM) cream of which trade name, Effaclar duo (+). They were prescribed to apply the cream twice a day for 60 days on the affected area on the face or other body area (if necessary). Patient was advised to used sunscreen daily during study period. The evaluation of tolerance and efficacy of Effaclar Duo (+), targeting both inflammatory and retentional types of lesions, and preventing colored marks, was assessed at inclusion (D0) and on the evaluation day (D60) using various outcome parameters. These parameters included acne severity (evaluated

Table 1 Global Evaluation Acne (GEA) scoring system.

Description	Score
No lesions, residual pigmentation may exist.	0
Hardly any lesion, rare dispersed open or closed comedones and rare papule.	1
Mild, easily identifiable: less than of the face is affected, some open or closed comedones and some papulo-pustules.	2
Moderate, more than half of the face is affected, numerous papulo-pustules, numerous open or close comedones, one nodule may exist.	3
Severe, the whole face is affected, covered with numerous papulo-pustules, open or closed comedones and rare nodules.	4
Very severe, very inflammatory acne covering the whole face with nodules.	5

using the GEA scoring system), the level of seborrhea (on a scale from 0 indicating absence to 10 indicating high presence), skin-colored marks (both erythema and pigmentation on a scale from 1 to 10), and the Cardiff Acne Disability Index (CADI) obtained through questionnaires to measure the patients' quality of life (QOL). The patient demographic profile, data on acne onset duration, and skin phototype were collected at D0, and a skin clinical examination was performed on both D0 and D60. Patients' compliance with the treatment was assessed using a study questionnaire at D60. Tolerance to the investigational product (IP) was evaluated by both the treating dermatologist and the patient through questionnaires, which were rated on a scale from low to excellent. Additionally, global satisfaction with the IP was assessed by both the dermatologist and the patient, ranging from very satisfied to very unsatisfied. Mean reduction rate for quantitative variables is calculated as (mean v0 - mean v1) /mean v0) *100. The response rate for qualitative variables was calculated as the percentage of patients with improvement. Response rate for tolerance is the percent of patients declaring the tolerance high or excellent.

Results

Demographic and Clinical Profile

A total of 268 patients were included in the study with female patients (76.4%) were predominance over male patients (23.6%). The mean age was 24.4±7.8 years old, ranged from 14 to 45 years old and 54.9% aged 24 years old and below. The mean duration acne from onset was 4.5±5.8 years and the mean age of acne onset was 20.3±7.3 years old. The Fitzpatrick skin type (FPT) distribution among cohort was 34.2 % with I-III, 51.3% with IV and 14.6% with phototype V. Majority (51.2%) were diagnosed with mixed type of acne followed by inflammatory (28.3%) and retentional acne (20.5%). Patient demographic and clinical data of the study is shown in **Table 2.**

Treatment of Acne

A total of 176 patients (71.5%) received Effaclar duo (+) cream as an adjunctive therapy to a topical or oral treatment while 70 patients (28.5%) received Effaclar duo (+) cream alone, as seen in **Figure 2**. The majority (58.9%) had already received at least one topical treatment, including topical retinoids (32.1%) and topical benzoyl peroxide (21.5%). Additionally, a few patients (2%) had received chemical peeling. At least one oral treatment was prescribed to 43.5% of the patients, with the majority receiving tetracycline/ doxycycline (39%), while some received other types of antibiotics (3.7%). Only a few (0.4%) received oral contraceptive pill. The mean duration of Effaclar duo (+) cream application among patients was 51.7±10.4 days, with 86.2% applying it twice a day to the face while the rest applied once per day, either in the morning

(10.2%) or at night (3.6%). Recommended concomitant daily sunscreen application was adhered in 88% of patients.

Table 2 Patients demographic and clinical profile (N=268).

Variable	Mean	Percentage (%)
Age (years)	24.4 ±7.8	
< 18		23.8
18-25		31.1
≥ 25		45.1
Gender		
Male		23.6
Female		76.4
Skin Phototype (Fitzpatrick)		
FPT I -III		34.2
FPT IV		51.3
FPT V		14.6
Acne duration (years)	4.5 ± 5.8	
Age of acne onset (years)	20.3 ±7.3	
Acne type		
Retentional		20.5
Inflammatory		28.3
Mixed		51.2

Clinical Efficacy Outcomes

For the severity of acne, of the 243 patients, at study enrolment or inclusion, 53.5% had mild acne severity (GEA 2), 37.4% had moderate (GEA 3) and 9.1% had hardly any active acne (GEA 1) at D0. However, only 190 patients completed GEA scoring at both visits and such numbers were analysed **(Figure 3)**. At D60, there was statistically significant ($p<0.0001$) improvement of the GEA Grade in 48% of the patients. The mean seborrhea score at D0 was 4.9±2.2. A significant ($p < 0.0001$) reduction of up to 46.9% in the seborrhea level was observed at D60, reaching a score of 2.5±2.1 **(Figure 4)**. At study enrolment, most (95%) patients reported presence of residual-coloured marks on their faces. At D60, a significant reduction ($p=0.0008$) changes of residual-coloured marks on the face, either pigmented or erythematous or both, were observed with 11.4% reported no coloured marks compared to 5.0% at inclusion. Significant improvement and disappearance ($p < 0.0001$) of erythematous and pigmentary marks were seen in 43.5% and 42.0% of patients respectively as seen in **Figure 5** and **Figure 6**.

Quality of Life Outcomes

Analysis of 201 patients showed a significant improvement ($p < 0.0001$) in QOL, with a 27.5% reduction in CADI score, from 5.9±3.2 at D0 to 4.2±3.0 at D60. The percentage of patients expressing non-concern or not at all, not bothered or not a problem for questions in CADI questionnaires increased at D60 compared to D0 **(Table 3)**, as follows: aggressive, frustrated, embarrassed (19.4% to 30.3%); social life impaired (37.8% to 49.8%); avoiding public changing facilities or swimsuit (60.6% to 67.9%); feelings about the appearance of the skin (11.4%to 24.4%); and perception of acne (8% to 15.4%).

Global Satisfaction and Tolerance (Safety) Assessment

The majority of dermatologists (77%, N= 193) and patients (77%, N=183), reported being very satisfied or satisfied with the efficacy of Effaclar Duo (+) cream. In terms of tolerance, 54% (N= 232) of dermatologists and 50% (N=222) of patients reported high to excellent levels.

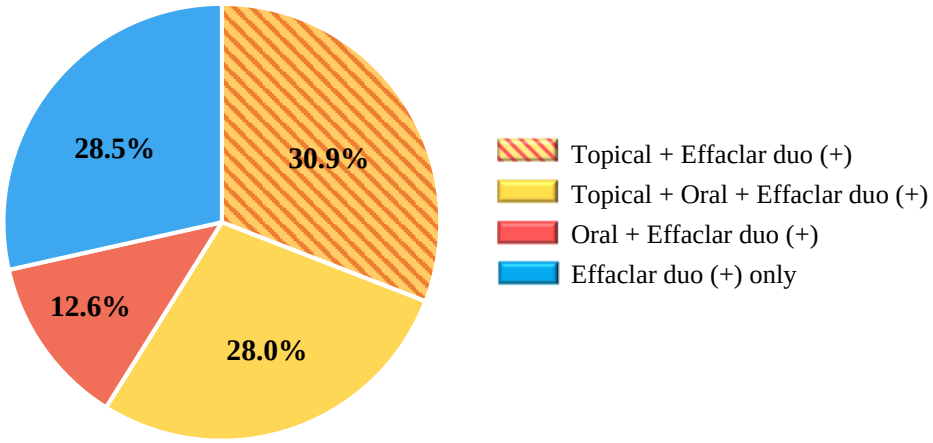

Figure 2 Summary of acne treatments received by patients (N=246).

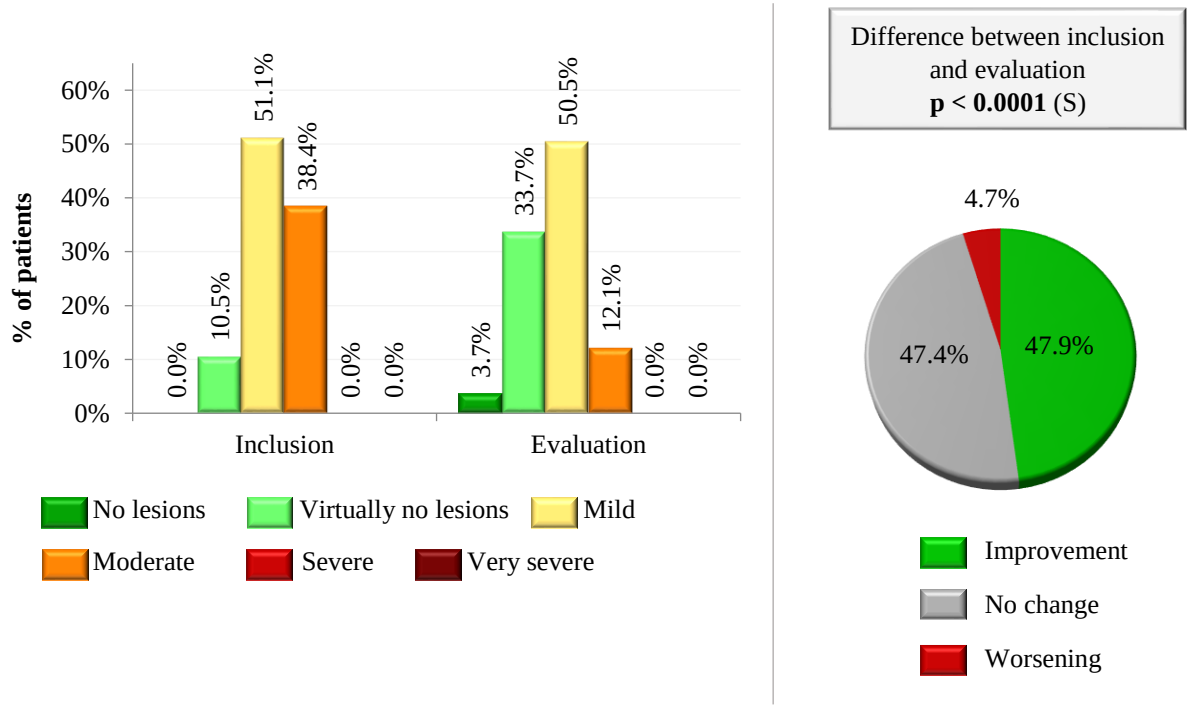

Figure 3 Severity of acne by GEA Score at inclusion (D0) and evaluation (D60); 0-No lesion; 1- Virtually no lesions; 2- Mild; 3- Moderate; 4-Severe; 5- Very severe; N=246.

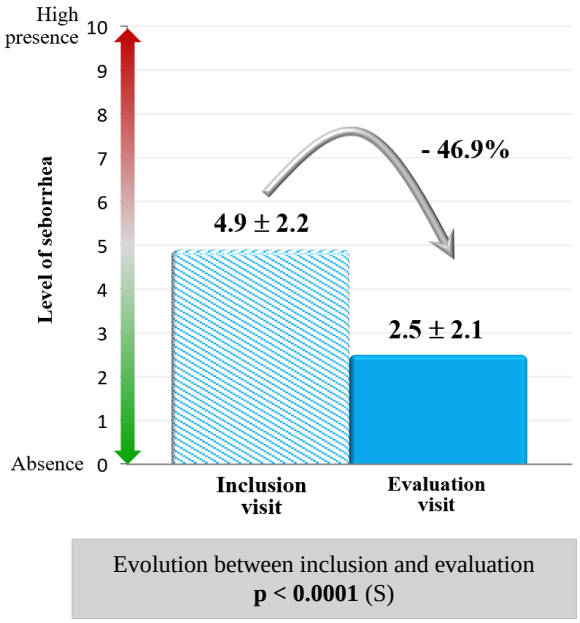

Figure 4 Levels of seborrhea at inclusion (D0) and evaluation(D60); N=246.

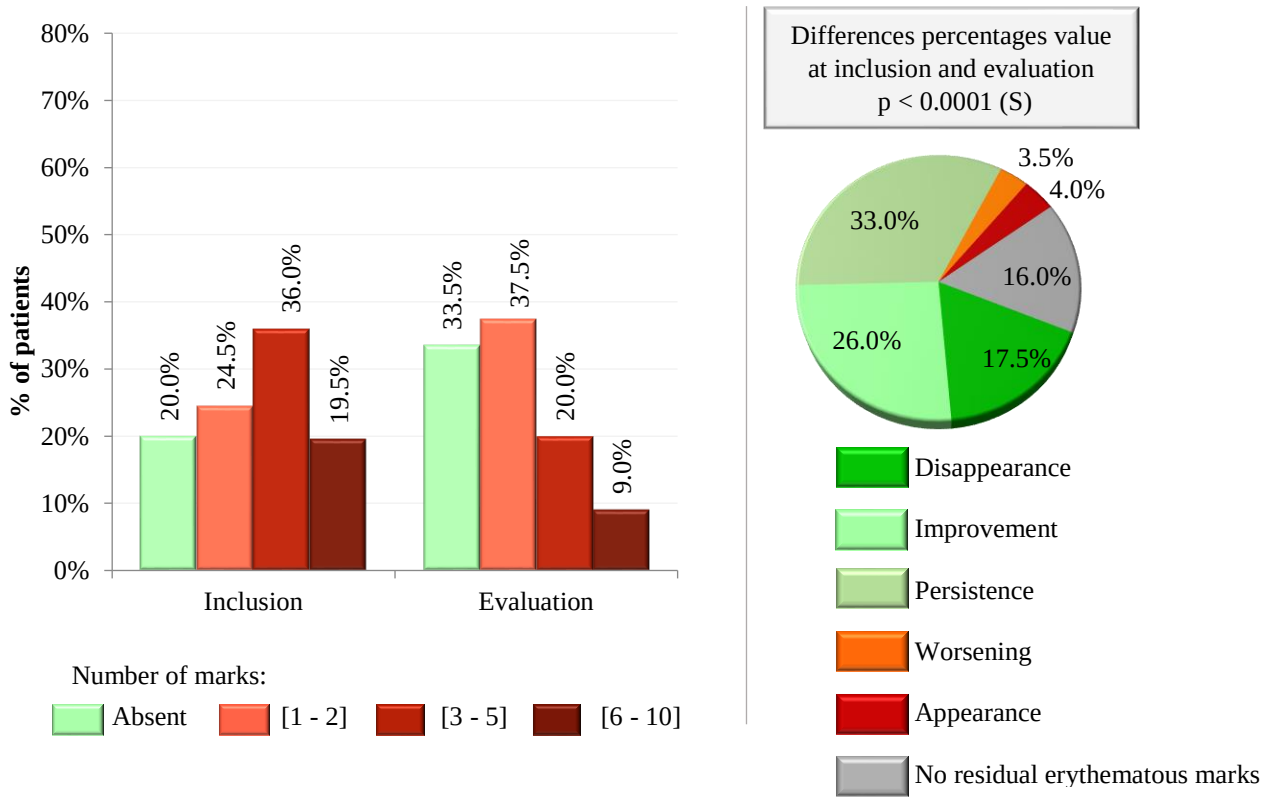

Figure 5 Erythematous marks assessment at inclusion (D0) and evaluation (D60); N=200.

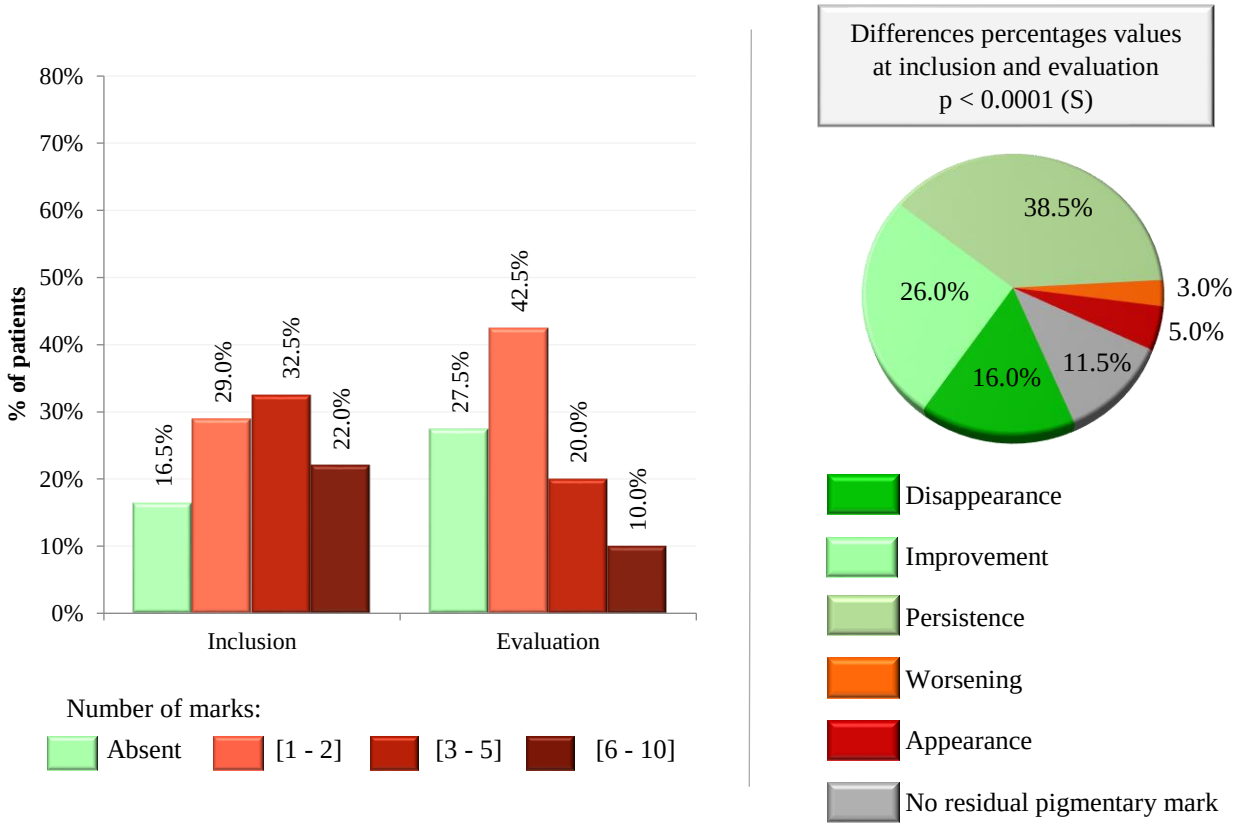

Figure 6 Pigmentary marks assessment at inclusion (D0) and evaluation(D60); N=200.

Table 3 CADI score

	Mean	Percentage (%)	
CADI score (N=201)			
D0	5.9 ± 3.2		
D60	4.2 ± 3.0		
CADI parameters		**Not at all/ Not bothered**	
		D0	**D60**
Aggressive, frustrated, embarrassed (N=201)		19.4	30.3
Social life impaired (N=201)		37.8	49.8
Avoiding public changing, facilities or swimsuit (N=193)		60.6	67.9
Feelings about the appearance of the skin (N=201)		11.4	24.4
Perception of acne (N=201)		8.0	15.4

Discussion

Acne is a chronic inflammatory disease of the pilosebaceous unit. It is divided into two categories, non-inflammatory (closed and opened comedone) and inflammatory (papule, pustule, cystic, nodule). A humid ASEAN country provides a challenge in treating patients with acne-prone skin. Despite the environment humidity, moisturizer application is still important in restoring natural skin barrier. Recent published data had shown the role of cutaneous microbiome

in the pathogenesis of acne [2,6]. Therefore, rebalancing the natural microbiome of the skin is essential in treating inflammatory skin disease. A topical moisturiser that maintains good skin barriers while correcting skin disequilibrium, which do not cause antibiotic resistance, and regulating quantity and quality of sebum, would be an ideal acne adjuvant treatment [6,7-10].

Generally, Asian skin is more prone to irritation to certain topical agents compared to other skin types, most notably, Caucasian skin [7,10]. Asian skin was reported to have an elevated neurosensory response to insults when compared to the skin of Caucasians. Asian skin has also been observed to be more prone to develop post-inflammatory hyperpigmentation, when inflamed or injured due to its relatively increased level of melanin pigmentation. Malaysia has diverse group of individuals, within multi-ethnicities, predominance of Malay ethnicity followed by the Chinese and Indian, resulted in the variability of skin FPT of which mostly ranging from Type III to V. It is unknown whether there are different in skin barrier strength, degree of maturation or degree of skin sensitivity within the different ethnic in Malaysia. Moreover, it is postulated that different subsets of Asian subjects may react differently to topical agents [11]. Despite the climate humidity, moisturising the skin is very essential to Asian skin. The results from this study showed that high tolerance to Effaclar duo (+) were observed, among patients with acne in Malaysia. Effaclar duo (+) with its non-greasy formulation provided the required moisturiser to patient of which help to overcome the side effects of dryness and stinging sensation associated with certain acne treatment such as topical retinoids and benzyl peroxide, thus improving compliance to treatment [12-17]. All patients had complied to minimum daily application, and none had applied more than twice a day.

Other than that, our study results demonstrate that Effaclar duo (+) significantly improved the GEA score and post-inflammatory hyperpigmentation among patients at D60. Similar results were found in a previous single-center, double-blind randomized trial in China, involving individuals with FPT phototype III to IV, which reported a significant reduction in inflammatory acne lesions in 58% of patient and a decrease in post-inflammatory hyperpigmentation by 42% [13]. However, the study conducted on 15 patients, utilized half-face comparisons (Effaclar Duo (+) versus placebo) and assessed outcomes through both clinical scoring and instrumental analysis during a similar study period.

The main bacterium involved in the pathogenesis of acne is *C. acnes* [1,18-19]. An increase in sebum creates an appropriate environment within the pilosebaceous unit for *C. acnes* proliferation. In this study, Effaclar Duo (+), which contains zinc pyrrolidone carboxylic acid (PCA) and niacinamide, has been found to significantly reduce seborrhea levels by up to 47%. This reduction eventually inhibits *C. acnes* proliferation, leading to an improvement in acne. Another noteworthy fact is that *Staphylococcus* is overexpressed on the surface of acne-prone skin [1-2,20-21]. The overexpression of *Staphylococcus* leads to the activation of keratinocyte toll-like receptors, which results in an increase in the production of cytokines and antimicrobial peptides, thus causing an increase in skin inflammation and worsening clinical signs of acne. Effaclar Duo (+) contains an active ingredient, Aqua Posae, in thermal spring water (APF). Aqua Posae is a derived lysate of the non-pathogenic *V. Filiformis* grown in La Roche-Posay thermal spring water [4-5,22-23]. *V. Filiformis* is killed by boiling and fragmented to prevent the risk of bacterial overproliferation, thus having postbiotic properties. The thermal spring water has a unique mineral and microbial composition (ranging from probiotic to prebiotic) and has been reported to significantly decrease *Staphylococcus* colonization in atopic patients with *S. aureus* overproliferation. Aqua Posae favors the growth of commensal bacteria and increases the synthesis of antimicrobial peptides

in the skin.

A significant improvement of 27.5% in the CADI score was reported in our study. This improvement may be attributed to improvement in both the GEA score and seborrhea score within the study cohort. The reduction of skin seborrhea played an important role in improving female QOL, with or without acne. A European study reported that female using regular skincare regime to reduce skin oiliness was able to improve the QOL by 24 % after 2 months of the treatment regime [12]. Seborrhea has been theorized to contribute to the progression of microcomedones into other types of acne lesions. Additionally, it provides a growth medium for *C. acnes*, allowing them to hydrolyze triglycerides in sebum, utilizing it as a nutrient source to produce free fatty acids and glycerol. Regulating both the quantity and quality of sebum presents a significant challenge in the treatment of acne.

Another factor that significantly affects QOL is acne recurrence. Dreno et al [24] reported that acne recurrence has caused 35.2% of subjects to express feelings of fatality. Hence, it is essential to optimize acne treatment, particularly in depressed-prone patients, with systemic and topical treatments. The treatments that ideally incorporate moisturizer regimens with added anti-inflammatory, skin barrier, and microbiota correction such as Effaclar duo (+) will bring benefits to the patients. Moreover, rebalancing the natural microbiome of the skin by restoring the natural skin barrier would eventually limit the proliferation of *P. acnes* on the skin [3,6,23]. Additionally, this study cream does not contain antibiotics, thereby reducing the risk of microbial resistance.

In conclusion, Effaclar Duo (+) cream demonstrated effectiveness and excellent tolerability as a standalone treatment or in combination with topical or systemic approaches for patients with mild to moderate acne in Malaysia. It successfully alleviated skin acne severity, post-inflammatory erythema, pigmentation, and hyper-seborrhea, ultimately improving the quality of life for patients with FPT phototype IV and mild to moderate acne within 60 days of application.

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References

1. Dréno B. What is new in the pathophysiology of acne, an overview. Journal of the European Academy of Dermatology and Venereology. 2017;31(Suppl 5):8-12.
2. Rocha M, Bagatin E. Skin barrier and microbiome in acne. Archives of Dermatological Research. 2018;310:181-5.
3. Huang C, Zhuo F, Han B, Li W, Jiang B, Zhang K, et al. The updates and implications of cutaneous microbiota in acne. Cell & Bioscience. 2023;13(1):113.
4. Zeichner J, Seite S. From probiotic to prebiotic using thermal spring water. Journal of Drugs in Dermatology. 2018;17(6):657-662.
5. Mahe YF, Perez M-J, Tacheau C, Fanchon C, Martin R, Rousset F, et al. A new Vitreoscilla filiformis extract grown on spa water-enriched medium activates endogenous cutaneous antioxidant and antimicrobial defenses through a potential Toll-like receptor 2/protein kinase C, zeta transduction pathway. Clinical, Cosmetic and Investigational Dermatology. 2013;6:191-196.
6. Dréno B, Dagnelie MA, Khammari A, Corvec S. The skin microbiome: a new actor in inflammatory acne. American Journal of Clinical Dermatology. 2020;21(Suppl 1):18-24.
7. Goh CL, Noppakun N, Micali G, Azizan NZ, Boonchai W, Chan Y, et al. Meeting the challenges of acne treatment in Asian patients: a review of the role of dermocosmet-

ics as adjunctive therapy. Journal of Cutaneous and Aesthetic Surgery. 2016;9(2):85-92.
8. Araviiskaia E, Lopez Estebaranz JL, Pincelli C. Dermocosmetics: beneficial adjuncts in the treatment of acne vulgaris. Journal of Dermatological Treatment. 2021;32(1):3-10.
9. Saint-Jean M, Khammari A, Seite S, Moyal D, Dreno B. Characteristics of premenstrual acne flare-up and benefits of a dermocosmetic treatment: a double-blind randomised trial. European Journal of Dermatology. 2017;27(2):144-149.
10. Andriessen A, Jiang X, Kulthanan K, Lee CH, Sinclair R, Zhang CF. Recommendations for using over-the-counter products as adjunctive acne care in asian phototypes: improving treatment outcomes and managing side effects. Journal of Drugs in Dermatology. 2021;20(11):1213-1221.
11. Alexis AF, Woolery-Lloyd H, Williams K, Andriessen A, Callender VD, Kang S, et al. Racial/ethnic variations in acne: implications for treatment and skin care recommendations for acne patients with skin of color. Journal of Drugs in Dermatology. 2021;20(7):716-725.
12. Segot-Chicq E, Compan-Zaouati D, Wolkenstein P, Consoli S, Rodary C, Delvigne V, et al. Development and validation of a questionnaire to evaluate how a cosmetic product for oily skin is able to improve well-being in women. Journal of the European Academy of Dermatology and Venereology. 2007;21(9):1181-1186.
13. Li L. A double-blind, randomized, placebo controlled clinical bilateral trial evaluating the efficacy and safety of a new formulation in acneic patients with risks of post-inflammatory hyperpigmented lesions. Poster session presented at 23rd European Academy of Dermatology & Venereology Congress, Amsterdam, NL. 2014;October 8-12.
14. Chien AL, Tsai J, Leung S, Mongodin EF, Nelson AM, Kang S, et al. Association of systemic antibiotic treatment of acne with skin microbiota characteristics. Journal of the American Medical Association (JAMA) Dermatology. 2019;155(4):425-434.
15. Kelhälä HL, Aho VT, Fyhrquist N, Pereira PA, Kubin ME, Paulin L, et al. Isotretinoin and lymecycline treatments modify the skin microbiota in acne. Experimental Dermatology. 2018;27(1):30-36.
16. Draelos ZD, Shalita AR, Thiboutot D, Oresajo C, Yatskayer M, Raab S. A multicenter, double-blind study to evaluate the efficacy and safety of 2 treatments in participants with mild to moderate acne vulgaris. Cutis 2012;89(6):287-293.
17. Angelova-Fischer I, Rippke F, Fischer T, Neufang G, Zillikens D. A double-blind, randomized, vehicle-controlled efficacy assessment study of a skin care formulation for improvement of mild to moderately severe acne. Journal of the European Academy of Dermatology and Venereology. 2013;27 (Suppl 2):6-11.
18. Park S-Y, Kim HS, Lee SH, Kim S. Characterization and analysis of the skin microbiota in acne: impact of systemic antibiotics. Journal of Clinical Medicine. 2020;9(1):168.
19. Ryan-Kewley AE, Williams DR, Hepburn N, Dixon RA. Non-antibiotic isotretinoin treatment differentially controls Propionibacterium acnes on skin of acne patients. Frontiers in Microbiology. 2017;8:1381.
20. Coughlin CC, Swink SM, Horwinski J, Sfyroera G, Bugayev J, Grice EA, et al. The preadolescent acne microbiome: a prospective, randomized, pilot study investigating characterization and effects of acne therapy. Pediatric Dermatology. 2017;34(6):661-664.
21. Dreno B, Martin R, Moyal D, Henley JB, Khammari A, Seité S. Skin microbiome and acne vulgaris: Staphylococcus, a new actor in acne. Experimental Dermatology. 2017;26(9):798-803.
22. Gueniche A, Knaudt B, Schuck E, Volz T,

Bastien P, Martin R, et al. Effects of non-pathogenic gram-negative bacterium Vitreoscilla filiformis lysate on atopic dermatitis: a prospective, randomized, double-blind, placebo-controlled clinical study. British Journal of Dermatology. 2008;159(6):1357-1363.
23. Nakatsuji T, Gallo RL. Dermatological therapy by topical application of nonpathogenic bacteria. Journal of Investigative Dermatology. 2014;134(1):11-14.
24. Dreno B, Bordet C, Seite S, Taieb C. 'Registre Acné'Dermatologists. Acne relapses: impact on quality of life and productivity. Journal of the European Academy of Dermatology and Venereology. 2019;33(5):937-943.

ORIGINAL ARTICLE

Safety and Efficacy of Combination 10 Sessions of Q-switched Nd:YAG 1064 nm and Pulsed Dye Laser 595 nm for Melasma Treatment Among Chinese Women in Malaysia.

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Abstract: Melasma is an acquired disorder of facial symmetrical hyperpigmentation due to multiple photomechanical factors. Evidence revealed that treating melasma should be able to target both the hyperpigmentation and the vascular anomalies to overcome the problems related to therapeutic efficacy and safety. The current study aimed to evaluate the safety and effectiveness of combination therapy involving Q-switched Nd: YAG 1064 nm and Pulsed Dye Laser 595 nm in the Chinese population in Malaysia with Fitzpatrick skin phototypes type III to IV. This study involved a retrospective study among 27 Chinese female patients associated with melasma and treated with ten sessions of a combination treatment at three weekly intervals from January 2022 to December 2022. The clinical photographs were examined to assess the mMASI score between the 1st, 5th and 10th treatment's visits. Statistical analysis revealed a significant effect of combination treatment on the mMASI scores reduction across the visits from the 1st visit (8.74±2.95), 5th visit (6.33±2.60), and 10th visit (6.00±3.21). There was a significant difference between the 1st and 5th visit ($p < 0.001$) and between the 1st and 10th visit ($p<0.001$). However, no significant difference was observed between the 5th and 10th visits ($p>0.05$). In terms of treatment's adverse reactions, most patients did not exhibit any adverse reaction (n=19, 70.4%), and only the minority of them demonstrated redness (n=1, 3.7%) and hyperpigmentation (n=7, 25.9%) following the combination treatment. The combination of 10 sessions of Q-switched Nd: YAG 1064 nm and Pulsed Dye Laser 595 nm was proven effective and safe on Chinese female patients with melasma with Fitzpatrick skin phototypes type III to IV.

Keywords: Chinese, Female, Melasma, Pulsed dye laser 595 nm, Q-switched Nd:YAG 1064 nm, Combination treatment, Ten sessions

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Introduction

Melasma is an acquired disorder of symmetrical hyperpigmentation of the face that commonly affects women with Fitzpatrick skin phototypes III to V living in areas of intense ultraviolet (UV) light exposure [1]. In a randomized study involving self-reporting of melasma in a Hispanic female population in 2007, Werlinger et al [2] noted the prevalence to be 8.8%. In Southeast Asia, the prevalence is as high as 40% in females [3]. The Chinese population in Malaysia is also at risk of developing melasma due to their exposure to intense UV rays, similar to other ethnic groups

[4]. Therefore, undoubtedly, melasma would pose an increasingly important skin disorder in the Malaysian population. Furthermore, the pathophysiology of melasma is multifactorial, resulting in treatment resistance and high recurrence rates.

In 2021, Artzi et al [5] conducted a review of 76 relevant articles and identified five main pathomechanisms in melasma: (1) melanocyte inappropriate activation; (2) aggregation of melanin and melanosomes in dermis and epidermis; (3a) increased mast cell count and (3b) solar elastosis; (4) altered basement membrane; and (5) increased vascularization. Additionally, Kim et al [6] suggested that the increased vascularization observed in melasma lesion was due to elevated angiogenic expression of vascular endothelial growth factor (GF) in melasma.

The treatment of melasma ranges from pharmacologic therapy to interventions with chemical peels, laser, and light therapy. Due to the complexity of its pathogenesis, it is even more challenging in skin phototype Fitzpatrick Type III to IV. Despite better photoprotection provided by increased melanin and more dispersed melanosomes in the skin of color, the treatment challenge persists due to photodamage and the risk of post-inflammatory hyperpigmentation (PIH) associated with cutaneous laser therapies. Hence, careful selection of laser devices and treatment parameters is necessary to minimize complications. Ideally, a wide variety of pathomechanisms should be addressed separately with multiple treatment regimens and sessions to maximize results.

Several studies are using different treatment modalities to treat melasma. Most lasers and laser-based combinations have been associated with reduced Melasma Area and Severity Index (MASI), such as the low-fluence Q-switched 1064 nm Nd:YAG laser, fractional ablative CO2 laser, and fractional ablative 2940 nm Er:YAG laser. One significant type of laser most commonly used for treating melasma is the Q-switched Nd:YAG in toning mode, which produces pulses with an extremely high peak of energy delivered in a short time (nanoseconds). This results in the destruction of melanin by a photoacoustic effect. This subcellular selective photothermolysis targets intracellular melanosomes, leading to less inflammation and, consequently, fewer post-inflammatory dyschromia [7]. Therefore, using low-fluence Q-switched Nd:YAG in toning mode with 0.5-1.0 Joules would further reduce the risk of post-inflammatory dyschromia in Fitzpatrick skin phototypes III to IV.

Kim et al [6] have also found that melasma lesions show significant vascularity with increased expression of vascular endothelial growth factor (VEGF), a major angiogenic factor of the skin in altered vasculature of melasma lesions. The systematic review of PubMed, EMBASE, and Cochrane done by Masub et al [8] in 2020 reported five articles (two randomized controlled trials (RCT), one retrospective review, and two case reports) that described the therapeutic effects of pulsed-dye laser (PDL) 595 nm to target the vascular component of melasma. Other than that, a split-face RCT of 17 patients found that PDL with daily triple combination therapy (TCT: hydroquinone, tretinoin, and fluocinolone) was more effective and could prevent melasma relapses than TCT alone [7]. Another retrospective review conducted in 2016 evaluated the efficacy of melasma treatment with PDL and low-power fractional diode laser (1927 nm). The author reported that more than half (54%) of patients showed more than 50% improvement in melasma [9]. Therefore, targeting the angiogenic factor of melasma lesions is crucial, and one approach involves using a 595 nm PDL in combination with the Q-switched Nd:YAG in toning mode.

Pulsed-dye laser is considered a gold-standard laser therapy for cutaneous vascular lesions, and it has been shown to be an effective treatment option when combined with pigment-targeted modalities for melasma patients in several studies [10]. However, only few published papers have been found in the literature utilizing a combination of Q-switched Nd:YAG at 1064 nm

and PDL at 595 nm in individuals with Fitzpatrick skin phototypes III to IV [10-12]. Therefore, a retrospective study was conducted among the Malaysian population receiving melasma treatment using a combination of low-fluence Q-switched Nd:YAG at 1064 nm and PDL at 595 nm. The aim of this study is to assess the safety and effectiveness of a treatment regimen consisting of 10 sessions of combined therapy using Q-switched Nd:YAG at 1064 nm and PDL at 595 nm for treating melasma in Chinese women living in Malaysia. This approach is intended to provide a comprehensive solution addressing the root causes of melasma.

Materials and Method

Study Design and Population

This study is a retrospective study among Chinese patients with melasma treated with a combination treatment of low fluence Q-switched Nd:YAG 1064 nm and PDL 595 nm between January 2022 and December 2022 at UR KLINIK in Malaysia. Patients were approached to obtain their consent for the treatment and research study. The methods and data collection in this study adhere to ethical standards. The ethics application for the study was obtained from the Hospital UMRA Medical Research Ethics Committee (UMRA-MREC:UMRA MREC003-23). The software G*Power, version 3.1.9.7, was used to determine the sample size with an effect size (partial eta squared: 0.6). Patient's medical records were screened for inclusion and exclusion criteria to identify eligible patients for the study. A thorough screening and review of the patient's medical records and data were conducted to ensure the inclusion and exclusion criteria were met.

The patient's medical records were included if the patient is:

a) Malaysian female of Chinese ethnicity with hyperpigmented skin lesions.
b) Age 40 years old to 60 years old.
c) Fitzpatrick skin phototype III to IV.
d) Undergone 10 sessions of combination low fluence Q-switched Nd: YAG 1064 nm and PDL 595 nm treatment within the study period.

The patient's medical records were excluded if:

a) They contained low-quality photographs (e.g. blurry).
b) They were incomplete or missing patient data such as demographics data, photos, parameters data, and consent forms for the treatments.

The electronic patient management systems were used to identify all patients who had undergone combination treatment of low fluence Q-switched Nd:YAG 1064 nm and PDL 595 nm treatments at UR KLINIK during the study period. The patients underwent a total of 10 sessions with an average interval of four to five weeks between treatments for the combination treatment administered by certified medical aestheticians. The laser settings for the Q-switched Nd:YAG 1064 nm were as follows: 1) Frequency 10Hz, 2) Spot size -8mm, 3) Fluence 0.5-1.0J/cm2. Meanwhile, the laser settings for PDL 595 nm were: 1) Frequency 2 Hz, 2) Spot size -5 mm, 3) Fluence 0.15-0.3 J/cm^2. The patient's medical photographs were examined to assess the improvement in melasma using the modified Melasma Area Severity Index (mMASI) score between the 1st, 5th, and 10th visits. The mMASI score provides a quantitative measurement of the severity of melasma. To minimize potential bias, the mMASI score was assessed by two groups of certified aesthetic doctors with two doctors in each group. The confidentiality of personal data, medical records, and photography was strictly maintained throughout the study.

Measuring Tools

In our study, we have adopted the globally recognized mMASI as the primary assessment tool to evaluate the efficacy of the low fluence Q-switched Nd: YAG 1064 nm and PDL 595 nm in

the management of melasma between the 1st, 5th and 10th visits. The mMASI score was used to calculate the severity of the condition based on two factors: the area of involvement and the darkness of the pigmented areas. The mMASI score **(Figure 1)** assesses four areas of the face - forehead, left and right cheeks, and chin whereas the size of the pigmentation is measured on a scale ranging from 0 (no involvement) to 6 (pigmentation covering 90 - 100% of the area). The darkness of the pigmented area was scored visually, ranging from 0 (no pigmentation) to 4 (pigmentation visible). The area and darkness scores for each facial region were multiplied to obtain that region's score, and the total mMASI score was obtained by adding up the scores for all four facial areas. The mMASI score formula was calculated as follows; [0.3A (forehead) x D(forehead) + 0.3A (Left malar) x D (left malar)] + [0.3A (right malar) x D (right malar) + 0.1 x A(chin) x D (chin)]. The total mMASI score ranges from 0 to a maximum of 24, with a higher score indicating more severe melasma. No prior research has documented an investigation into the assessment of treatment efficacy for melasma utilizing the mMASI score in conjunction with a combination of low fluence Q-switched Nd: YAG 1064 nm laser and PDL 595 nm throughout multiple treatment sessions.

The evaluation of the study relied on subjective assessment based on before and after photographs taken from five different angles, as shown in **Figure 2**. All the doctors from the two groups received a two-hour training on the evaluation of facial appearance according to the mMASI score. Each group consists of at least one certified License of Credentialing and Privileging (LCP) doctor. The two groups of doctors evaluated the mMASI score using patients' photographs from the 1st, 5th, and 10th visits, as shown in **Figure 3A, 3B** and **3C**. In situations where there are discrepancies in the mMASI scores, discussions were initiated to facilitate consensus and agreement on the final mMASI score. Any adverse reactions from the start of the treatment until completion were recorded and analyzed.

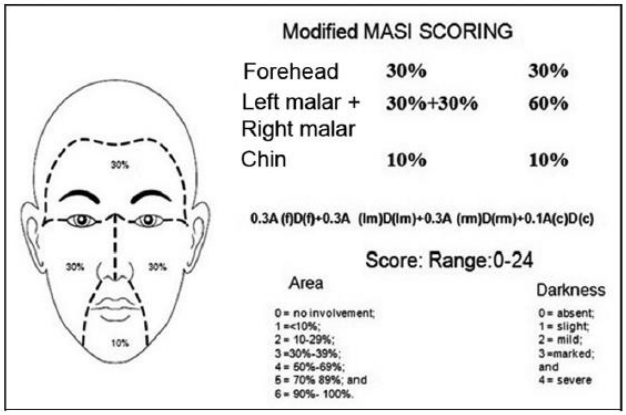
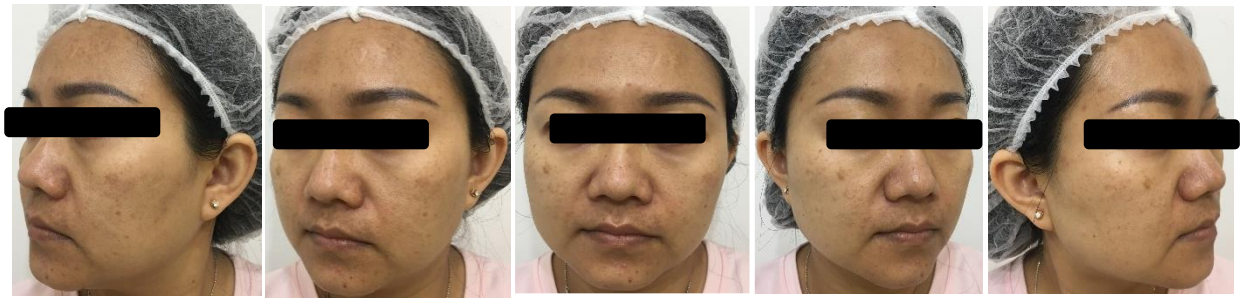


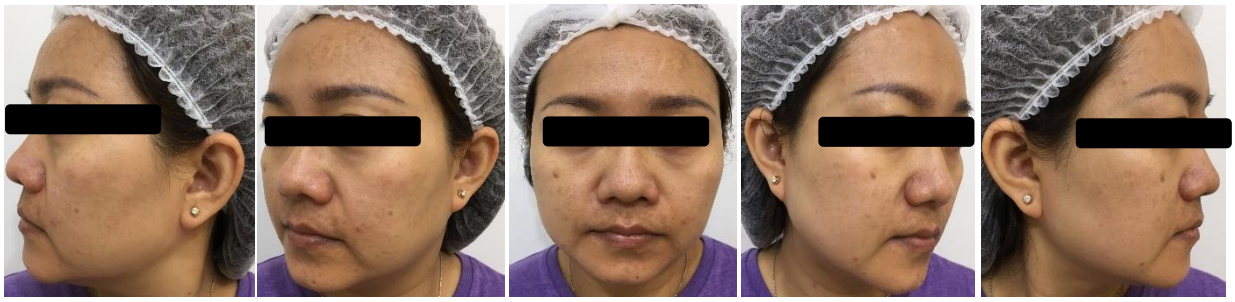
Figure 1 mMASI score [13].

Figure 2 Five different angles photograph [14].

1st visit



5th visit



10th visit

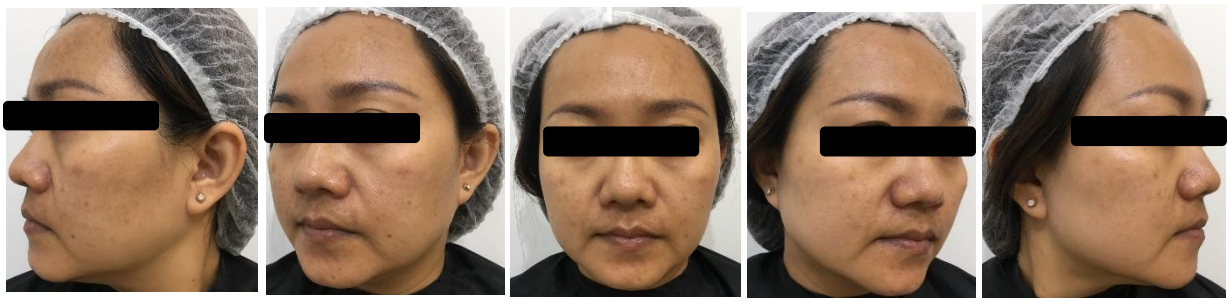
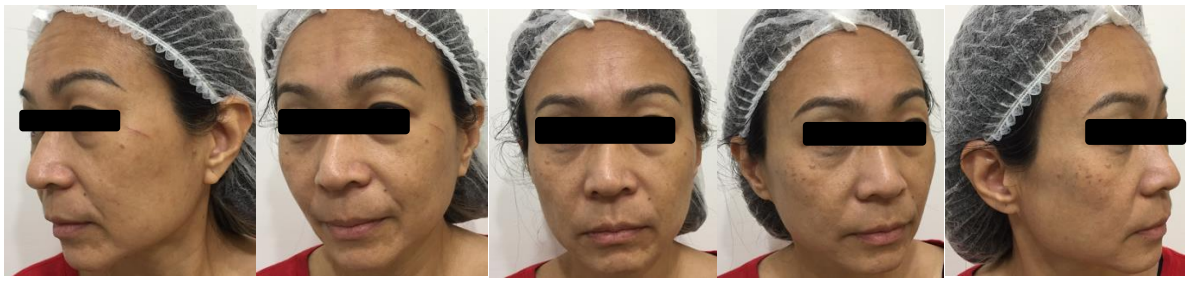
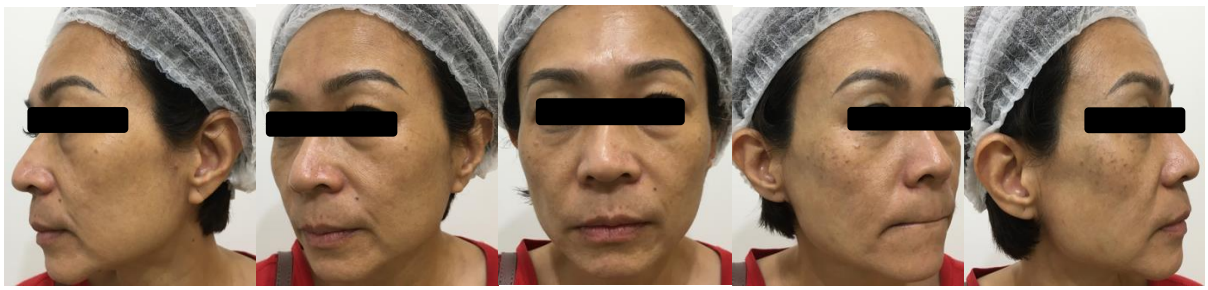


Figure 3A Patients' picture across visits. Treatment progress of a Chinese patient with Fitzpatrick III to IV over 1st, 5th, and 10th visits, respectively.

1st visit



5th visit



10th visit

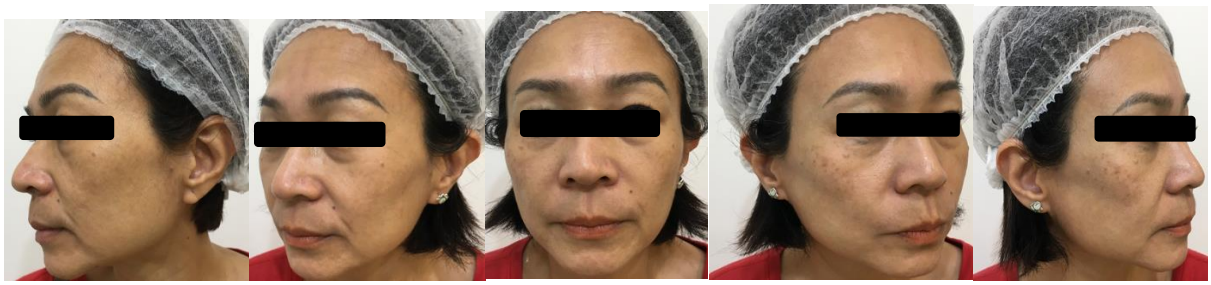
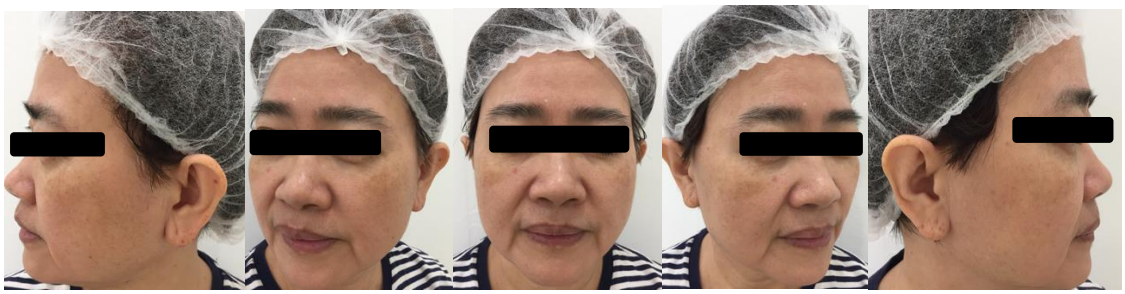
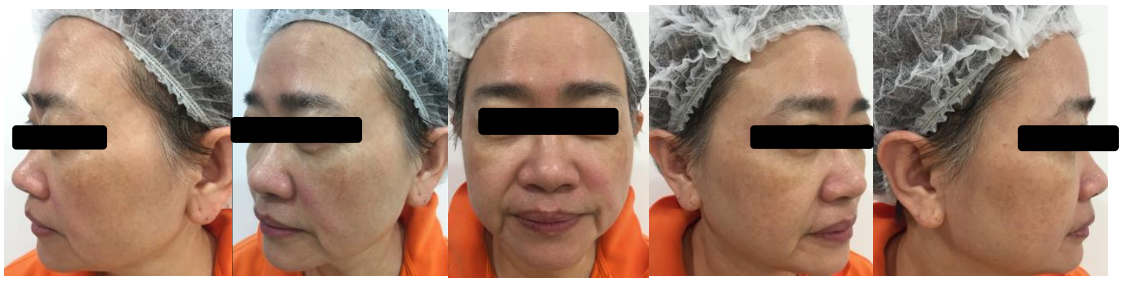


Figure 3B Patients' picture across visits. Treatment progress of a Chinese patient with Fitzpatrick III to IV over 1st, 5th, and 10th visits, respectively.

1st visit



5th visit



10th visit

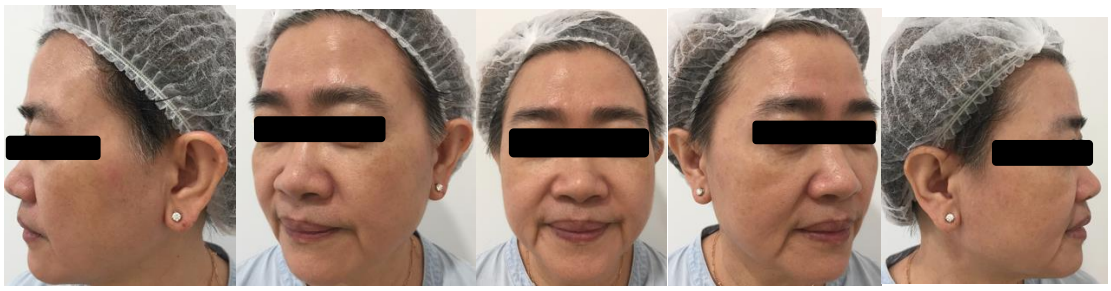


Figure 3C Patients' picture across visits. Treatment progress of a Chinese patient with Fitzpatrick III to IV over 1st, 5th, and 10th visits, respectively.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) version 23.0 was applied for descriptive and inferential statistical tests. The descriptive analysis details patients' demographic data, reported as numbers, percentages, mean± standard deviation (SD), where appropriate. A repeated measure Analysis of Variance (ANOVA) was performed to compare and evaluate the treatment outcomes using the mMASI score between the 1st visit, 5th visit, and 10th visit. The significant level will be set at a p-value < 0.05.

Results

A total of 27 patients medical records were included in the study after screening based on the inclusion and exclusion criteria. The current study revealed that the mean age of the patients was 47.70±4.58, while most patients were between 41-45 years old (44.4%). The patients included individuals with Fitzpatrick Skin Type III (n=14, 51.9%) and Fitzpatrick Skin Type IV (n=13, 46.4%). This study noted that the majority of the patients have melasma with freckles (n=11, 48.1%), followed by those who have melasma

with solar lentigines (n=5, 18.5%) and melasma with bilateral nevus of ota like macules (n=2, 7.4%). However, only nine patients (33.3%) have melasma without other hyperpigmentation types. When the treatment's adverse reactions in each visit were evaluated, it was found that the majority of them did not show any adverse reaction (n=19, 70.4%), and the minority of them showed redness (n=1, 3.7%) and hyperpigmentation (n=7, 25.9%) from the combination treatment. For the patient experiencing redness (n=1, 3.7%), 1% hydrocortisone was administered, and the patient was advised to rest for one month before reassessment of the face. Following this intervention, the redness completely resolved. Regarding patients who developed hyperpigmentation (n=7, 25.9%), the majority encountered this issue between the fifth and eighth treatment sessions, coinciding with their perimenopausal age range of 45 to 55 years old. The management strategy for these individuals included counseling of adherence to broad-spectrum sunblock and extending the treatment interval to five to six weeks. As a result, patients observed a reduction in hyperpigmentation. The patient's demographics and clinical profile is summarized in **Table 1**.

Table 1 Patients demographic and clinical profile (n=27).

Variables	n (%)		Mean ± SD
Age (years)			
40-45	12	(44.4)	47.70 ± 4.58
46-50	5	(18.5)	
51-55	9	(33.3)	
56-60	1	(3.7)	
Skin Fitzpatrick Type			
Type III	14	(51.9)	
Type IV	13	(48.2)	
Other Type of Pigmentation			
Bilateral Nevus of Ota-like Macules	2	(7.41)	
Freckles	11	(40.7)	
Solar Lentigines	5	(18.5)	
No other pigmentation	9	(33.3)	
Adverse Reaction			
Redness	1	(3.7)	
Hyperpigmentation	7	(25.9)	
Nil (No adverse effects)	19	(70.4)	

Additionally, using the repeated measure ANOVA, the result showed a statistically significant effect of combination treatment on the mMASI score among patients across the visits, $F(1.62, 42.12) = 22.07$, $p < 0.001$, partial $\eta_p^2 = 0.46$. The current study observed a significant reduction in the mean mMASI score across visits from the 1st visit (8.74±2.95), 5th visit (6.33±2.60), and 10th visit (6.00±3.21). A post hoc pairwise comparison with Bonferroni adjustment indicates a significant difference in the mMASI score between the 1st visit and 5th visit ($p < 0.001$) and between the 1st visit and the 10th visit ($p<0.001$). However, no significant difference was observed between the 5th and 10th visits ($p>0.05$). The mean and SD of the mMASI score across visits are presented in **Table 2**.

Table 2 Mean difference of patients' mMASI score across treatment visits.

Visit Treatment	Mean±SD	Comparison Visit	p-value
1st Visit	8.74 ± 2.95	1st visit - 5th visit	0.000
5th Visit	6.33 ± 2.60	5th visit - 10th visit	0.373
10th Visit	6.00 ± 3.21	1st visit - 10th visit	0.000

Discussion

Hyperpigmented skin lesions are frequently observed among the Chinese population. Among hyperpigmented skin lesions, melasma is a prevalent cutaneous disorder in Southeast Asia, with a prevalence ranging from 0.25% to 4% among individuals seeking medical attention in Dermatology Clinics [15]. Its highest incidence occurs in individuals aged 30 to 44, affecting individuals of all races and genders. It is more commonly observed in women with darker skin types falling within the Fitzpatrick skin types IV to VI. Hence, this study focuses on treating melasma in people with Fitzpatrick skin types III and IV between the ages of 40 and 60, with a higher incidence rate in the female gender.

It is noteworthy that melasma can exert a significant adverse impact on the quality of life of affected individuals, particularly in cases of severe manifestation [16]. Considering the significant societal contributions made by women in our modern context, our research study integrates the utilization of low fluence Q-switched Nd: YAG 1064 nm and PDL 595 nm for a safe and efficient treatment of melasma.

Melasma presents a challenge in treatment due to its complexity in the pathology of interactions between the keratinocytes, mast cells, gene regulation abnormalities, neovascularization, and disruption of basement membrane [17]. Various modalities have been employed in the treatment of melasma to target different pathology, and studies have reported that the low fluence Q-switched Nd: YAG is safe for melasma treatment, mainly when using the 1064 nm wavelength in low fluence [18]. However, since neovascularisation is one of the important factors in melasma pathogenesis and low fluence Q-switched Nd:YAG 1064 nm primarily targets melanin, PDL with a wavelength of 595 nm plays a role in treating the vessel abnormalities and has shown promise in treating the vascular component of melasma with a generally favorable safety profile [10]. Pulsed-dye laser targets oxy-hemoglobin in the blood vessels, leading to photothermolysis of the vessels supplying the melasma lesions. Thus, the combination of low fluence Q-switched Nd:YAG 1064 nm and PDL 595 nm might provide a comprehensive treatment targeting melasma's vascular and pigmented components.

In our study involving a female population from Malaysia, we identified a prevalent occurrence of melasma characterized by a mixed vascularization component. Remarkably, we observed a substantial enhancement in treatment effectiveness as evidenced by a noteworthy decrease in the mean mMASI score from the 1st visit to the 10th visit. This improvement was achieved by implementing a combination approach that effectively addressed melanin accumulation and heightened vascularization. Lee et al. [18] have conducted a comprehensive review of literature on publications from 2009 to 2022 for low fluence Q-switched Nd:YAG 1064 nm laser, including combination treatment, to evaluate the efficacy and adverse events. A systematic PubMed search was conducted, and 42 articles were included in the study. From the study, it was found that low fluence Q-switched Nd:YAG 1064 nm laser appeared to be a generally effective and safe treatment for melasma.

Both low fluence Q-switched Nd:YAG 1064 nm laser and PDL have a risk of post-inflammatory hyperpigmentation (PIH), especially in patients with darker skin types, if not used judiciously. Besides that, some common side

effects include transient erythema (redness) and purpura (purple or red-brown skin discolorations) after a PDL session. Proper patient assessment, treatment protocols, and post -treatment care (sunscreen application and hydration) are vital for safety and achieving the desired outcomes. Nevertheless, it is noteworthy that most patients in our study do not exhibit any adverse reactions to the treatment. Only a few patients developed erythema and hyperpigmentation.

In a previous study, researchers compared two treatments for melasma on a split-face basis: with PDL and 1064 nm Q-switch Nd:YAG laser on one side and only Q-switch Nd:YAG laser on the other. They found that both treatments led to a noticeable reduction in MASI scores on both sides of the face, and there were no significant differences in MASI score changes between the two treatments over the study duration. However, among the patients, seven individuals who had widened capillaries under dermoscopy experienced different MASI score improvements during treatment. It was noted that the use of Q-switched Nd:YAG 1064 nm laser alone on one side resulted in an increase in the MASI score during the follow-up period [10]. This suggest s that the PDL with Q-switched Nd:YAG 1064 nm laser treatment combination is particularly effective when melasma includes visible vascular lesions.

It is believed that VEGF and skin vascularization may play a role in melasma pigmentation [5]. Melanocytes, responsible for skin pigmentation, can respond to angiogenic factors because they have functional VEGF receptors. Vascular endothelial growth factor might directly influence melanocyte behavior through these receptors. Additionally, VEGF stimulates the release of arachidonic acid, which can impact melanin production. By targeting melasma's vascular lesions, PDL might limit melanocyte activation. Our study demonstrated a significant improvement of 27.57% in the mMASI score between the 1st and 5th visits, with a notable 31.45% improvement from the 1st visit to the 10th visit. However, the improvement decreased to 5.32% between the 5th and 10th visits. While we observed statistical significance in the improvement of the mMASI score before and after treatment, the varying outcomes between the 1st to 5th and 5th to 10th visits may be due to the heterogeneous nature of melasma.

Some studies suggest that the selective destruction of melanosomes with minimal damage to melanocytes is a key concept in this treatment, known as ‘subcellular selective photothermolysis’. This technique targets melanosomes, melanocytic dendrites, and subcellular melanin organelles, resulting in significant improvement from the 1st to the 5th visits. However, we hypothesize that the reduced improvement from the 5th to the10th visits may be due to dermal pathology and other factors not directly targeted by laser treatment. Additionally, this treatment not only effectively reduces mMASI scores during the treatment phase but also appears to help prevent relapse after treatment.

Ten sessions of a combinations of Q-switched Nd:YAG 1064 nm laser and PDL 595 nm using low fluence were recommended for the treatment of melasma among Chinese women in Malaysia, as it showed a significant difference in mMASI Score from the 1st to the 10th visits. Despite 25% of patients experiencing hyperpigmentation, a significant portion of them were in their perimenopausal age, during which hormonal fluctuations may occur. Hormones like estrogen and progesterone have been implicated in triggering melasma, with elevated levels correlating with increased skin pigmentation [19]. While complete avoidance of hyperpigmentation may be challenging, counseling on the consistent use of broad-spectrum sunscreen [20] and the addition of other treatment modalities such as polynucleotides [21] and energy-based devices [22] targeting additional photomechanisms of melasma, such as solar elastosis and altered basement membrane, can further help reduce its occurrence.

Limitation

This study is subject to several constraints. Firstly, the sample size employed in this investigation was relatively modest. Consequently, there is a need for future research endeavours to encompass larger sample sizes to yield a more comprehensive assessment of both treatment efficacy and safety. Secondly, the study's participant pool was exclusively composed of individuals from the Chinese ethnicity. Although the recruited Chinese patients exhibited Fitzpatrick skin types III and IV, the absence of patients from other ethnic backgrounds may limit the ability to fully generalize the findings regarding the combined treatment's effectiveness in addressing melasma across diverse ethnic groups. Additionally, the small sample size and reliance on scoring conducted from photographic images rather than clinical evaluation of the actual patients may introduce bias, especially in cases where patients have more than one pigmentary disorder. Future studies could incorporate a control group for comparison to assess the significant difference between the treatment group and the control group. Furthermore, conducting clinical assessments of actual patients followed by scoring based on clinical judgment would help reduce potential biases in the results.

Conclusion

Despite these limitations, this study offered innovative insights into the treatment of melasma. The combination of 10 sessions involving Q-switched Nd:YAG1064 nm and PDL 595 nm has demonstrated effectiveness and safety in treating melasma in individuals with Fitzpatrick skin types III to IV. Although the improvement diminishes between the 5th and 10th visits, the treatment remains safe as the adverse reaction observed is reversable and manageable. Based on our findings, we propose the potential use of additional therapies to target various aspects of melasma either before, during, or after the 5th laser session to optimize results. Further research will be essential to advance our understanding and management of melasma.

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Conflict of Interest

The authors declared no potential conflicts of interest for this article's research, authorship, and/or publication.

References

1. Sheth VM, Pandya AG. Melasma: a comprehensive update: part II. Journal of the American Academy of Dermatology. 2011;65(4):699-714.
2. Werlinger KD, Guevara IL, González CM, Rincón ET, Caetano R, Haley RW, et al. Prevalence of self-diagnosed melasma among premenopausal Latino women in Dallas and Fort Worth, Tex. Archives of Dermatology. 2007;143(3):423-31.
3. Sivayathorn A. Melasma in orientals. Clinical Drug Investigation. 1995;10:34-40.
4. Tian WC. Novel technique to treat melasma in Chinese: The combination of 2940-nm fractional Er: YAG and 1064-nm Q-switched Nd: YAG laser. Journal of Cosmetic and Laser Therapy. 2016;18(2):72-4.
5. Artzi O, Horovitz T, Bar-Ilan E, Shehadeh W, Koren A, Zusmanovitch L, et al. The pathogenesis of melasma and implications for treatment. Journal of Cosmetic Dermatology. 2021;20(11):3432-45.

6. Kim EH, Kim YC, Lee ES, Kang HY. The vascular characteristics of melasma. Journal of Dermatological Science. 2007;46(2):111-6.
7. Cassiano DP, Espósito AC, da Silva CN, Lima PB, Dias JA, Hassun K, et al. Update on Melasma—part II: treatment. Dermatology and Therapy. 2022;12(9):1989-2012.
8. Masub N, Nguyen JK, Austin E, Jagdeo J. The vascular component of melasma: a systematic review of laboratory, diagnostic, and therapeutic evidence. Dermatologic Surgery. 2020;46(12):1642-50.
9. Geddes ER, Stout AB, Friedman PM. Retrospective analysis of the treatment of melasma lesions exhibiting increased vascularity with the 595-nm pulsed dye laser combined with the 1927-nm fractional low-powered diode laser. Lasers in Surgery and Medicine. 2017;49(1):20-6.
10. Kong SH, Suh HS, Choi YS. Treatment of melasma with pulsed-dye laser and 1,064-nm Q-switched Nd: YAG laser: a split-face st udy. Annals of Dermatology. 2018;30(1):1-7.
11. Lee YS, Lee YJ, Lee JM, Han TY, Lee JH, Choi JE. The low-fluence Q-switched Nd: YAG laser treatment for melasma: a systematic review. Medicina. 2022;58(7):936.
12. Cassiano DP, Espósito AC, da Silva CN, Lima PB, Dias JA, Hassun K, et al. Update on melasma—part II: treatment. Dermatology and Therapy. 2022;12(9):1989-2012.
13. Khurana VK, Misri RR, Agarwal S, Thole AV, Kumar S, Anand T. A randomized, open-label, comparative study of oral tranexamic acid and tranexamic acid microinjections in patients with melasma. Indian Journal of Dermatology, Venereology and Leprology. 2019;85:39.
14. Henderson CJ, Larrabee Jr WF, Krieger HB. Photographic standards for facial plastic surgery. Archives of Facial Plastic Surgery. 2005.
15. Achar A, Rathi SK. Melasma: a clinico-epidemiological study of 312 cases. Indian Journal of Dermatology. 2011;56(4):380.
16. Mpofana N, Paulse M, Gqaleni N, Makgobole MU, Pillay P, Hussein A, et al. The Effect of melasma on the quality of life in people with darker skin types living in Durban, South Africa. International Journal of Environmental Research and Public Health. 2023;20(22):7068.
17. Rajanala S, Maymone MB, Vashi NA. Melasma pathogenesis: a review of the latest research, pathological findings, and investigational therapies. Dermatology Online Journal. 2019;25(10).
18. Lee YS, Lee YJ, Lee JM, Han TY, Lee JH, Choi JE. The low-fluence Q-switched Nd: YAG laser treatment for melasma: a systematic review. Medicina. 2022;58(7):936.
19. Basit H, Godse KV, Al Aboud AM. Melasma. In: StatPearls [Internet]. Treasure Island (FL): StatPearls; 2023.
20. Fatima S, Braunberger T, Mohammad TF, Kohli I, Hamzavi IH. The role of sunscreen in melasma and post inflammatory hyper-pigmentation. Indian Journal of Dermatology. 2020 ;65(1):5-10.
21. Cavallini M, Bartoletti E, Maioli L, Massirone A, Pia Palmieri I, Papagni M, et al. Consensus report on the use of PN-HPT™(polynucleotides highly purified technology) in aesthetic medicine. Journal of Cosmetic Dermatology. 2021;20(3):922-928.
22. Reynal S, Martin E, Munavalli G. Energy-based devices for melasma and post inflammatory hyperpigmentation. Dermatological Reviews. 2023;4(1):58-66.

CASE REPORT

Papular Granuloma Annulare: Rare Variant of a Common Disease Entity

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Abstract: Granuloma annulare is a rare cutaneous granulomatous disease of uncertain etiology, often characterized by ringed or annular papules or plaques. Here, we present a case of a 9-year-old Filipino girl with asymptomatic bilateral skin-colored papules on her elbows. The patient's mother had attempted self-medication with cashew-based cream, which yielded no improvement. Physical examination revealed well-defined papules, and laboratory tests showed neutrophilia, lymphopenia, and normal metabolic profile. A skin biopsy confirmed the diagnosis of papular granuloma annulare, characterized by granuloma formation with increased mucin deposition. Treatment with topical clobetasol propionate resulted in remarkable improvement. However, the patient was subsequently lost to follow-up. This case underscores the atypical presentation of granuloma annulare in a pediatric Asian patient and highlights the importance of considering this diagnosis in unusual cases.

Keywords: Granuloma annulare, Papular variant, Case report, Dermatopathology

Introduction

The epidemiologic data available for granuloma annulare is sparse and limited, it has been said that the prevalence is between 0.1 to 0.4%. Granuloma annulare is described as a cutaneous granulomatous disease with an unknown etiology. It has been proposed that association was seen in infection, metabolic diseases, and trauma [1]. Granuloma annulare is usually benign and thought of as self-limited when not associated with serious conditions such as malignancy or HIV [2]. Granuloma annulare as the name suggests commonly presents clinically as a ringed or annular papule or plaque with a granulomatous inflammation seen in histology. Over the decades, there have been atypical and rare variants described in the literature but the lack of large-scale case studies and confusing classification has made it difficult for proper classification [3].

Case Presentation

A 9-year-old female Filipino child presented to the clinic with a history of 1 year of asymptomatic bilateral skin-colored papules on the elbows. The patient's mother claims she was not seen by any other physician and has self-medicated with cashew-based cream, for which the said lesions were unresponsive to. The patient was otherwise normal and healthy with unremarkable past medical history. Physical examination revealed multiple well -defined skin-colored papules and plaques measuring 1 to 2 cm localized on bilateral

elbows **(Figure 1A, Figure 1B)**. The rest of the physical examinations were unremarkable with no affectation of the hair, nail, and mucosa. A complete blood count revealed neutrophilia (56.25%), lymphopenia (30.59%), and eosinophilia (3.42%). The metabolic panel was unremarkable except for a slightly elevated HbA1C (5.8%), patient was subsequently referred to pediatric services for further evaluation and management. A slit skin smear with an acid-fast smear was done with one of the lesions which revealed negative results. A 4 mm skin punch biopsy with a lesion on the right elbow stained with Hematoxylin and Eosin (H&E) was done and revealed a normal epidermis with a granuloma formation **(Figure 2A)**. On low power magnification (10x) of the H&E slide showed infiltrates surrounding degenerated collagen **(Figure 2B)** on high magnification (40x) confirms palisading lymphohistiocytic infiltrates **(Figure 2C)**. Special staining with alcian blue showed positive highlighting in the granuloma indicating increased mucin deposition **(Figure 2D)**.

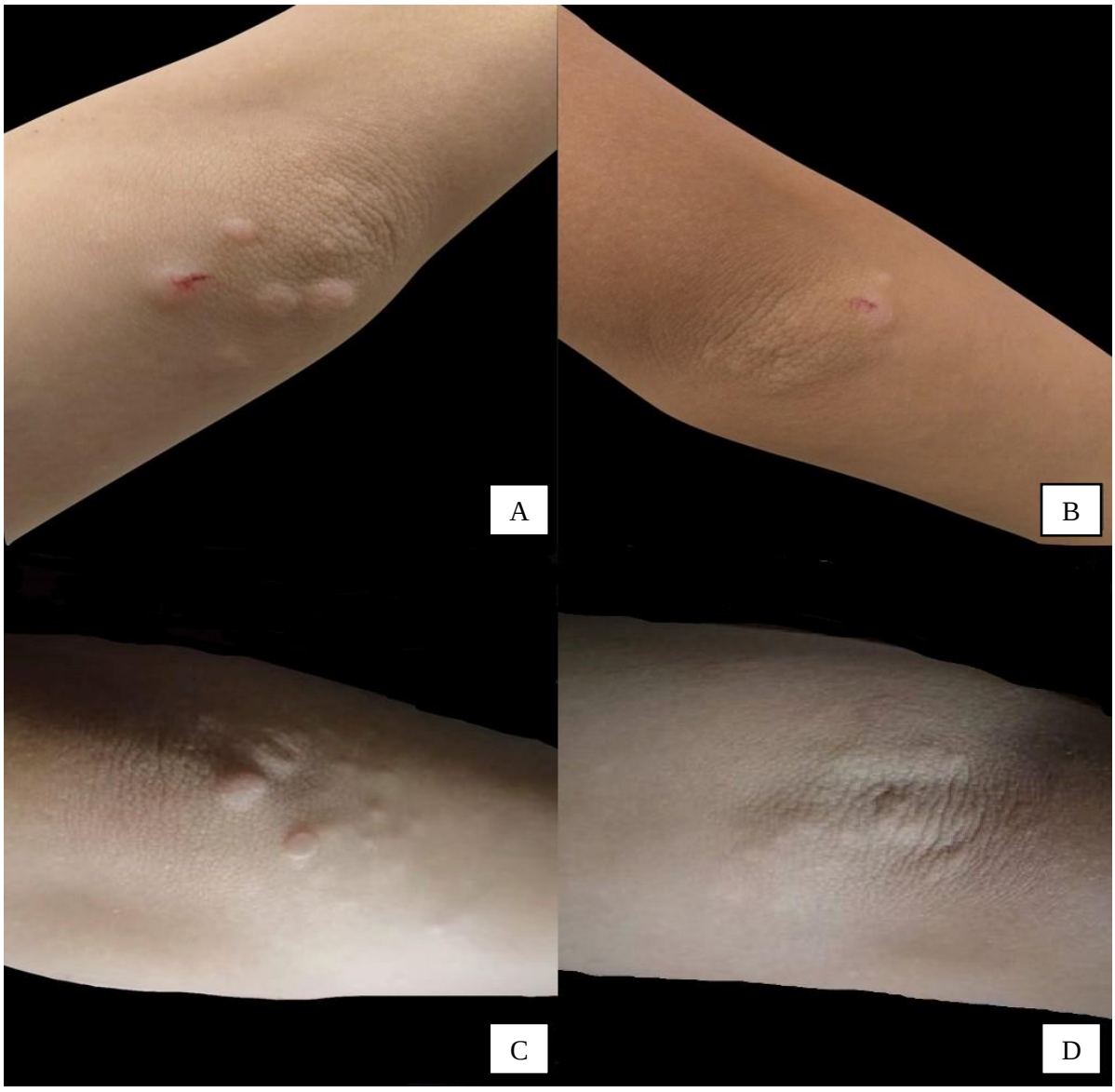

Figure 1 A; Left elbow **B**; Right elbow (Both showing multiple asymptomatic well-defined skin-colored papules and plaques measuring 1-2 cm). **C**; Left elbow **D**; Right elbow (Both showed improvement after 2 weeks of clobetasol propionate 0.05% ointment application). *Linear excoriation due to slit skin smear procedure done on the patient.

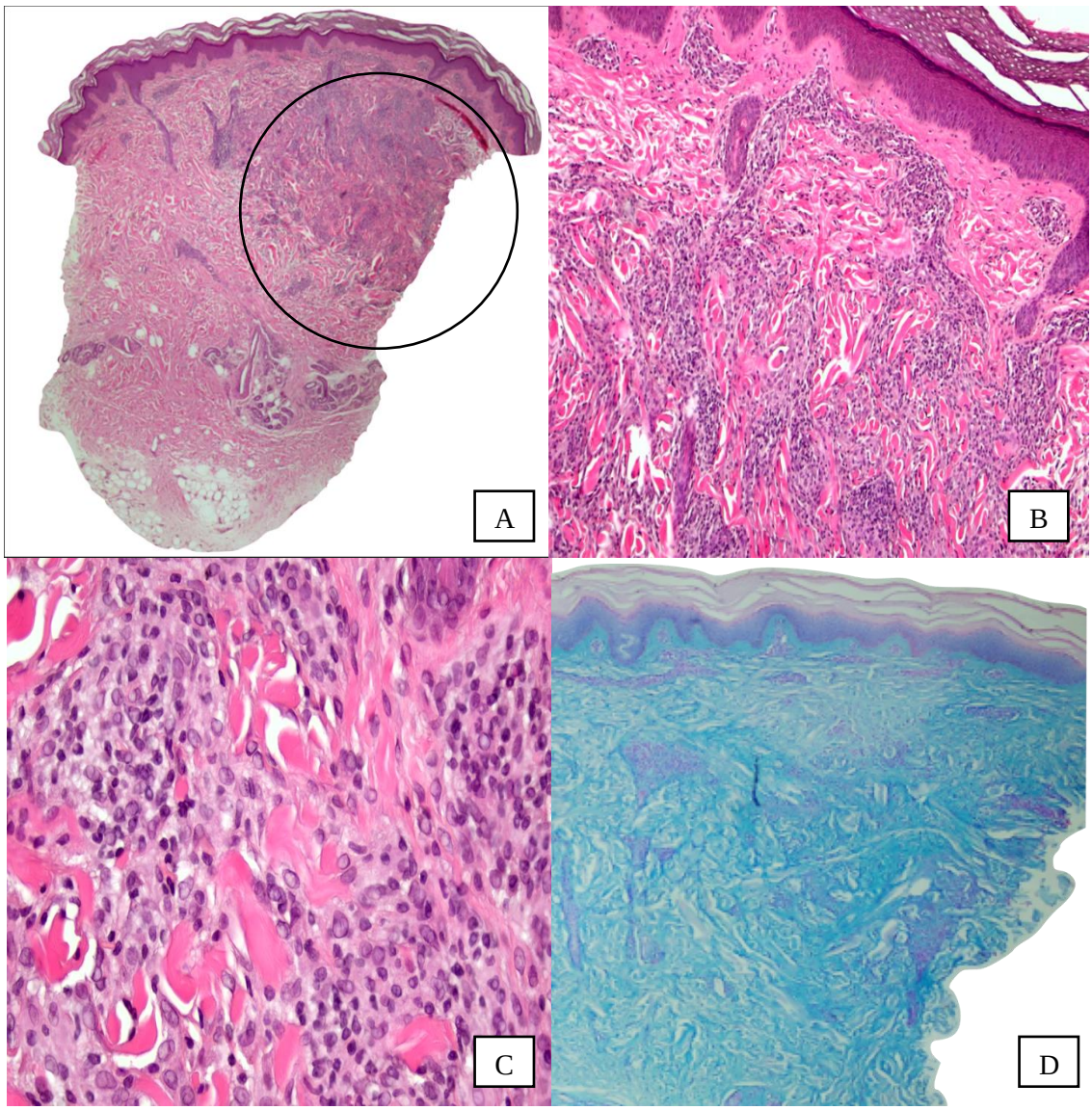

Figure 2 A; Scanning view(4x) of lesion stained with H&E showing granuloma formation highlighted by a black circle. **B**; Low power magnification (10x) of the H&E slide showing infiltrates surrounded by degenerated collagen. **C**; High power magnification of the H&E slide confirming predominance of lymphohistiocytic infiltrates. **D**; Scanning view(4x) of the same slide stained with alcian blue indicative of increased mucin content.

Management and Outcome

The patient was subsequently diagnosed as papular granuloma annulare and was started on topical clobetasol propionate 0.05% ointment for 2 weeks since the presentation of the lesions was localized. Upon follow-up 2 weeks later, the patient noted almost complete resolution of her cutaneous symptoms with only hypertrophic scarring of the previous biopsy site with no dyspigmentation **(Figure 1C, Figure 1D)**. The patient was advised to shift to tacrolimus 0.1% ointment for 2 more weeks but was subsequently lost to follow-up.

Discussion

Granuloma annulare is a relatively common disorder that presents more in white females in the third to fifth decade of life, although it could be noted that it is a rare finding in Black, Hispanic, and Asian individuals [4] which is an exception as our patient is an Asian child. Granuloma annulare has a prototypic classic variant of ringed or

arcuate erythematous plaques clinically. The presentation in this case is papules which have been previously reported by Smith [5] but has not been truly validated in large case series if truly a different distinct morphology of the disease This presentation appears more commonly as localized forms but can also present as generalized or disseminated if presenting with 10 or more widespread annular plaques. Based on morphology, there have been different reports of subcutaneous nodules, patches, umbilicated papules, and even pustules. Histologically, granuloma annulare presents with focal necrosis surrounded by a palisade of histiocytes. The hallmark of granuloma annulare is the finding of increased mucin deposition. Additional findings of multinucleated giant cells, eosinophils, lymphocytes, and neutrophils all have been reported. The important triad of degraded collagen, histiocytic infiltrate, and the presence of mucin have been indicative findings in all granuloma annulare subtypes [6].

There are a few differential diagnoses that should be considered in lesions presenting as asymptomatic skin-colored papules on the elbows. We list down some of which we considered for this case:

a) Papular sarcoidosis: Papular sarcoidosis is an idiopathic multisystem granulomatous illness, sarcoidosis typically affects the skin, lymph nodes, lungs, and eyes. Approximately two-thirds of patients are female, and the condition often manifests at age 40. There are different morphological presentations including: papules, micropapules, plaques, subcutaneous nodules, scar sarcoidosis, lupus pernio, erythema nodosum, ulceration [7]. Upon biopsy, histopathologic findings will include characteristic granulomatous inflammation is a well-defined chronic inflammatory process where the primary cell is an activated macrophage that resembles an epithelial cell, hence the term "epithelioid cell." A granuloma is a well-defined, well-organized region of granulomatous inflammation made up of lymphocytes, leukocytes, epithelioid cells, and occasionally plasma cells [8]. Papules tend to develop on the face (often around the eyes) or neck. These papules can be reddish brown, violet, tan, brown, or the same color as skin which makes it different from our patient's case.

b) Papular acrodermatitis of childhood: A benign rash known as papular acrodermatitis of childhood (Gianotti-Crosti syndrome) can develop in children as a result of certain viral infections and vaccines. Childhood papular acrodermatitis presents as an acral papular rash with accompanying systemic symptoms. Acute eruptions of monomorphic skin-colored to pink-red papules on the cheeks, buttocks, and extensor surfaces of the extremities are the hallmark lesions, which makes it different from our patient's case. Papular acrodermatitis of childhood has a non-specific histology. Para-keratosis and localized epidermal spongiosis are possible findings. In the papillary dermis, there might also be a perivascular, lymphocytic infiltration [9].

c) Tuberous xanthomas: Are benign plaques, papules, or nodules that form in the subcutaneous and cutis and are defined by a build-up of lipid-laden macrophages. Tuberous xanthomas typically measure no more than 2 cm and are observed in a number of lipidoses. Typically, they are suggestive of a disruption in lipoprotein metabolism, specifically familial hypercholesterolemia. Histopathological analysis typically reveals areas of fibrosis and cholesterol clefts, together with clusters of foam cells and lipid-laden macrophages [10].

d) Histoid leprosy: A rare kind of multibacillary leprosy known as histoid leprosy is characterized by the development of papules, plaques, or nodules that have an erythematous, skin-colored, or keloid-like appearance. The predominant histological characteristic is fusiform cells. Clinicians and pathologists face a diagnostic problem because it can mimic other dermatological lesions, such as dermatofibroma and neurofibroma. Histopathology is character-ized by an infiltrate that is primarily made up of fusiform histiocytes, which resemble fibroblasts and can occasionally resemble a fibrohistiocytic tumor. It is also associated with a large number of

acid-fast bacilli and a small number of foamy macrophages [11].

In literature, it has been mentioned that patients presenting with granuloma annulare have a significant increase in associated autoimmune, diabetes mellitus, hyperlipidemia, hypothyroidism, and ischemic heart disease [12]. In our patient it was noted that she is otherwise normal for her age in terms of thyroid function and lipid levels, it was noted however that there is a slight elevation of her HbA1C but with normal fasting blood sugar levels [13]. Recently, according to the study of Emre et al [14], viral infections such as Epstein-Barr virus, human immunodeficiency virus, varicella-zoster virus, and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been described to cause granuloma annulare as well.

Granuloma annulare is benign and often self-limited. Numerous treatment regimens have been reported in treating this disease entity, which include topical and systemic steroids, psoralen UV-A, isotretinoin, dapsone, pentoxifylline, hydroxychloroquine, cyclosporine, interferon-gamma, chlorambucil, potassium iodide, nicotinamide, niacinamide, salicylic acid, chlorpropamide, thyroxine, dipyridamole, methyl aminolevulinate photodynamic therapy, fumaric esters, etanercept, infliximab, adalimumab, and efalizumab [15]. In our patient, it was decided that it would be optimal to start on topical corticosteroid since the patient presented with a localized form of granuloma annulare for which the patient responded positively with noted improvement in terms of regression of size of previously seen lesions and was planned to shift to a topical calcineurin inhibitor, however patient was lost to follow up.

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References

1. Schmieder SJ, Harper CD, Schmieder GJ. Granuloma annulare. StatPearls Publishing; 2020.
2. Imadojemu S, Rosenbach M. Advances in inflammatory granulomatous skin diseases. Dermatologic Clinics. 2019;37(1):49-64.
3. Piette EW, Rosenbach, M. Granuloma annulare: Clinical and histologic variants, epidemiology, and genetics. Journal of the American Academy of Dermatology. 2016;75(3):457-465.
4. Barbieri JS, Rodriguez O, Rosenbach M, Margolis D. Incidence and prevalence of Granuloma Annulare in the United States. JAMA Dermatology. 2021;157(7):824-830.
5. Smith S. Localized papular Granuloma annulare in an adult: A new clinical variant? Journal of the American Academy of Dermatology. 2014;70(5): AB117.
6. Joshi TP, Duvic M. Granuloma annulare: An updated review of epidemiology, pathogenesis, and treatment options. American Journal of Clinical Dermatology. 2021;23: 37-50.
7. Reddy RR, Shashi Kumar, BM, Harish MR. Cutaneous sarcoidosis - a great masquerader: a report of three interesting cases. Indian Journal of Dermatology. 2011;56(5):568-572.
8. Tana C, Donatiello I, Caputo A, Tana M, Naccarelli T, Mantini C, Ricci F, Ticinesi A, Meschi T, Cipollone F, Giamberardino MA. Clinical features, histopathology and differential diagnosis of sarcoidosis. Cells. 2021;11(1): 59.
9. Snowden J, Rice AS, O'Shea NE. Papular acrodermatitis. StatPearls Publishing; 2023.
10. Babu R, Venkataram A, Santhosh S, Shivaswamy, S. Giant tuberous xanthomas in a case of type IIA hypercholesterolemia. Journal of Cutaneous and Aesthetic Surgery.

2012;5(3):204-206.
11. Fernandes TRMO, Andrade, VJS, Nascimento ID, Matias, AKS. Histoid leprosy presenting as a large tumor. Anais Brasileiros de Dermatologia. 2021;96(6):759-761.
12. Leasure AC, Damsky W, Cohen J.M. Comorbidities associated with granuloma annulare: A case-control study in the All of Us research program. Journal of the American Academy of Dermatology. 2022;87(1):197-199.
13. Pinhas-Hamiel O, Hamiel U, Boyko V, Graph-Barel C, Reichman B, Lerner-Geva L. Trajectories of HbA1c levels in children and youth with type 1 diabetes. PLoS One. 2014;9(10):e109109.
14. Emre S, Unal E, Celik B, Sungu N. The case of granuloma annulare associated with SARS-CoV-2 infection. Dermatologic Therapy. 2022;35(5).
15. Garg S, Baveja S. Generalized granuloma annulare treated with monthly rifampicin, ofloxacin, and minocycline combination therapy. Indian Journal of Dermatology. 2013;58(3):197.

CASE REPORT

Combination Therapy of Fractional Laser and Subcision for Acne Facial Scarring

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Abstract: Acne vulgaris is a prevalent skin disease that predominantly afflicts adolescent populations. Permanent scarring from acne is an unfortunate complication of acne vulgaris. Atrophic acne scars are more common than hypertrophic or keloid scars and are generally classified as ice pick, boxcar, or rolling scars. Having acne scars can be emotionally and psychologically distressing to patients. In this case report, we presented a case of a 26-year-old lady with Fitzpatrick skin type IV and a combination of scars including rolling scars, box scars and ice pick scars over her face. She was treated with three sessions of treatments with 3-week interval between sessions. The first session was a combination treatment of subcision and Fractional CO2 laser. The next two treatments were single treatments of only Fractional CO2 laser. In this study, we intend to discuss the multimodal treatments for facial scarring.

Keywords: Atrophic acne scar, Subcision, Fractional CO2 laser

Introduction

Acne vulgaris is a prevalent skin disease that predominantly afflicts adolescent populations [1]. It is caused and characterized by multiple factors including Propionibacterium acnes activity, increased sebum production, androgenic stimulation, follicular hypercornification, lymphocyte, macrophage and neutrophil inflammatory response, and cytokine activation [2]. Inflammatory acne lesions can result in permanent scars, the severity of which may depend on delays in treating acne patients [3]. Permanent scarring from acne is an unfortunate complication of acne vulgaris. Acne scars can be classified into three different types- atrophic, hypertrophic, or keloidal [4]. Atrophic acne scars are more common than hypertrophic or keloid scars and are generally classified as ice pick, boxcar, or rolling scars [1]. Ice pick scars are usually narrow (< 2 mm), deep, sharply demarcated tracts that can extend into the deep

dermis or subcutaneous tissue. Rolling scars are wider (4 to 5 mm) and shallower than ice-pick scars, producing an undulating appearance. Boxcar scars are wider at the base than ice-pick scars, do not taper, and can be shallow (<0.5 mm) or deep (>0.5 mm). Hypertrophic acne scars and keloids are characterized by excess collagen deposition, resulting in a raised papule or plaque.

Scars appearing on the face due to multiple reasons, mainly being acneiform scarring, often cause psychological, emotional and cosmetic problems to many people especially women. The purpose of minimally invasive treatments in aesthetic dermatology is to obtain better effects with as much smaller thermal trauma to the skin as possible, while keeping the epidermis intact. There are several multimodal treatments available for facial scarring due to acne.

Subcision

Subcision, also known as subcutaneous incision-less surgery, is a phrase that Orentreich and Orentreich first used in 1995 [5] to refer to a small surgical treatment for correcting depressed scars and wrinkles that involves inserting a tri-beveled hypodermic needle through a puncture in the skin surface (thus, "incisionless" surgery) and manipulating the needle's sharp edges to generate subcuticular cuts or "- cisions" underneath the defect. The goal of this surgery is to remove the fibrous threads holding the scar to the subcutaneous tissue beneath. The fibrotic attachments in the dermal-subcutaneous junction that pulls down the skin's surface are physically torn apart, making it more effective than other therapy procedures.

To maximise the outcomes of this procedure, numerous novel approaches have been created in recent years. Needles, cannulas, wires, and blunt-blade instruments are the four major types of subcision tools that are frequently used to treat atrophic acne scars. Use of these devices varies depending on scar depth, aesthetic preferences, and treatment combinations. However, each tool has its own advantages and also some complications which might follow. Initially subcision was done using hypodermis needle of different gauge thickness depending on the scar's depth, the thickness of its fibrotic tether, and practitioner's personal choice [6]. Then, several modifications have been done to improve the outcome of this procedure, including using a different type of needle such as the triangular tip Nokor needle as was reported by Jacob et al [7]. Subsequently, other tools have been used primarily cannula. However, there are limitations as subcision might only puncture the fibrotic tethers rather than completely severing them, thus, combination treatments will yield higher efficacy in treating acne scars.

Fractional CO2 Laser

Traditional ablative laser therapies have fallen out of favor in the treatment of atrophic acne scars despite their efficacy because of the higher incidence of side effects and longer downtime. Fractional laser treatments have become the gold standard of care. The carbon dioxide (CO2) laser in ablative fractional resurfacing (AFR) is now the most popular aesthetic treatment for skin beauty [8]. **Figure 1** illustrates the modes of a CO2 laser.

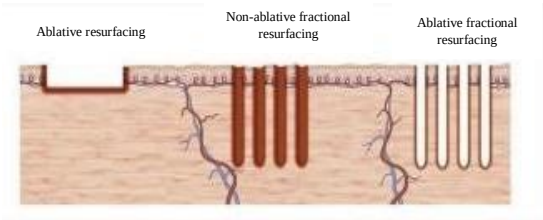

Figure 1 Modes of a CO2 laser.

The fractional carbon dioxide laser has a wavelength of 10,600 nm which has a strong absorption of water in human body. The concept of fractionated photothermolysis served as the foundation for the mechanism of the carbon dioxide laser. This method thermally ablates columns of the skin, leaving behind areas of healthy skin that quickly repopulate the columns of tissue that were removed. It is a laser emission mode that creates countless micro-heat treatment zones (MTZs) by emitting minute focal spots (50

to 80 μm) through highly focused mirrors. They are columns of repeated thermal injury that are divided by healthy skin tissue [9,10].

This is further supported by histologic evidence of wound repair, in which the retained keratinocytes accelerate the healing process of collagen synthesis, allowing for reepithelialization in less than 48 hours without compromising the epidermal barrier function. It is widely recognized that fractional carbon dioxide laser treatment is-associated with a significantly lower incidence of adverse effects and better safety profiles than typical ablative laser treatment. However, post-inflammatory hyperpigmentation (PIH) following fractional carbon dioxide laser resurfacing has frequently been a problem, particularly in individuals with darker skin [11].

Dermabrasion/Microdermabrasion

Dermabrasion and microdermabrasion are facial resurfacing techniques that mechanically ablate damaged skin in order to promote re-epithelialization. Dermabrasion completely removes the epidermis and penetrates to the level of the papillary or reticular dermis, inducing remodeling of the skin's structural proteins. Microdermabrasion, a more superficial variation of dermabrasion, only removes the outer layer of the epidermis, accelerating the natural process of exfoliation. Unlike dermabrasion, microdermabrasion can be repeated at short intervals. However, dermabrasion will not improve atrophic acne scars optimally [12].

Punch Excision for Ice Pick Scars

Another popular method of treating acne scars is punch excision. Deeply depressed acne scars with steep vertical walls, like ice pick and boxcar scars, can benefit from punch excision procedures. Since these scars reach the deep reticular dermis, resurfacing methods alone cannot be used to effectively treat them [13]. Punch instruments are circular blades that have a variety of diagnostic and therapeutic uses in several fields of medicine and surgery. This multifunctional punch blade is used during punch surgery (or biopsy) while the patient is under local anaesthesia [14]. There are different sizes of the instrument ideally in between 1.5 to 3.5 mm used according to the size of the acne scar. Using the concept of scar manipulation, in a punch excision, a large circular scar is removed and the skin is then sutured along the lines of reduced skin tension. This method effectively transforms a recessed scar or hole into a linear scar that is flat. The appearance of these flat linear scars can subsequently be minimized using laser resurfacing, which will be considerably more aesthetically pleasing. The modified scar that resulted would be flat and simple to cover up with a thin coat of foundation or cosmetics, thus will yield the best outcome for the patient.

Trichloroacetic Acid Cross

Another treatment for acne scar available is the CROSS technique (Chemical Reconstruction of Skin Scars). It is ideally suited to treat ice pick or small boxcar scars by using a high strength of the peeling agent, Trichloroacetic acid (TCA). The CROSS technique involves stretching the skin and using a small wooden toothpick to administer 50 to 100 percent TCA to the bottom of the ice pick scar, resulting in epithelial tract breakdown. This is followed by collagenization and filling of the depressed ice pick scar throughout the healing phase. Collagen synthesis can take two to three weeks and can last up to six weeks. This technique can be performed two or three times at an interval of two to four weeks [15].

Chemical Peeling

Chemical peeling is the process of applying chemicals to the skin to destroy the outer damaged layers, thus accelerating the normal process of exfoliation. There are multiple types of peeling agents that may vary in the depth of penetration. The classification of peeling agents is listed in **Table 1**.

Table 1 Classification of peeling agents [16].

Depth Of Penetration	Histologic Level	Peeling Agents
Very superficial	Destruction of the stratum corneum without creating a wound below the stratum granulosum.	• Glycolic acid, 30% to 50% applied briefly (1 to 2 minutes) • Jessner solution, applied in 1 to 3 coats • TCA 10%, applied in 1 coat
Superficial	Destruction of part or all of the epidermis, anywhere from the stratum granulosum to the basal cell layer.	• Glycolic acid, 50% to 70%, applied for a variable time (2 to 20 minutes) • Jessner solution, applied in 4 to 10 coats • TCA, 10% to 30%
Medium depth	Destruction of the epidermis and part or all of the papillary dermis.	• Glycolic acid 70%, applied for a variable time (3 to 30 minutes) • TCA, 35% to 50% • Augmented TCA (CO2 + TCA 35%; Jessner solution + TCA 35%; glycolic acid 70% + TCA 35%)
Deep	Destruction of the epidermis and papillary dermis, extending into the reticular dermis.	• Phenol 88% • Baker-Gordon phenol formula

Case Presentation

This is a case of a 26-year-old lady, with no known medical illness and no known drug allergy presented to an aesthetic clinic with a combination of post acne and chicken pox scars from 10 years ago. Her acne condition worsened during her late adolescence days as she was in college under a lot of stress coping with her studies and exams. Besides that, she is also very active in sports and usually spends more time outdoors exposed to the sun. Her daily skincare routine consists of cleanser, toner, moisturizer and sunscreen. She rarely uses serum and sheet masks. Her menstrual cycle was normal, all investigation was done and there was no evidence of autoimmune disease such as Polycystic Ovary Syndrome (PCOS). She was previously treated for her acne vulgaris condition with topical anti acne, adapalene gel, Cerave gel cleanser and completed two courses of systemic antibiotic treatment namely tablet doxycycline 100 mg once daily under a dermatology clinic follow up. Subsequently, her acne improved however she developed multiple acne scars all over her face.

As she entered adulthood and started working, she had an inferior complex regarding her facial scarring condition which she was unable to conceal with cosmetic products (e.g. concealer and foundation). This is when she decided to seek aesthetic treatments. On physical examination, her skin type was Fitzpatrick IV and there was a combination of scars predominantly ice picks scars and rolling acne scars over her face with hyperpigmentation **(Figure 2)** especially over the bilateral cheek.

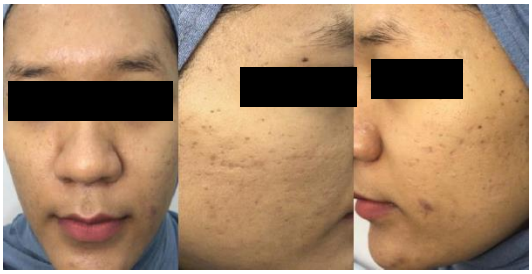

Figure 2 Before treatment.

Management and Outcome

The recommended procedure suggested by the doctor was combination treatment sessions of subcision over cheek and jaw area followed by fractional CO2 laser for her acne scarring. The patient underwent three sessions of treatments within 3-week intervals. The first session was a combination treatment of subcision and Fractional CO2 laser. Numbing cream was applied all over face for 30 minutes before beginning the subcision procedure. Cannula was used and was inserted at the right cheek adjacent to the scar parallel to the skin surface into deep dermis and moved back and forth in a fan like motion to release fibrous bands at dermal plane. The same procedure was repeated at the left cheek. After the subcision, laser procedure was started. Fractional CO2 laser (More Xel bison) was used, energy was set up to 5.0 mJ, density at 0.5. At the end of the treatment, a face mask was put on and a 3 days course of doxycycline antibiotics was prescribed to cover for bacterial infection. However, due to cost, the next two treatments were only single treatment which is the fractional CO2 laser. As for the setting, the energy was increased up to 5.2 mJ for the second session and 5.4 mJ for the third session. The density was also increased up to 1.0 for both sessions

The patient had a follow up after completing three sessions of treatments, claiming that the acne scars over the cheek areas are much improved however prominent ice pick scars are seen **(Figure 3, Figure 4, Figure 5)**. Further treatments such as combination of laser and TCA CROSS were suggested. The patient agreed to do it later as the downtime usually takes 3 to 7 days.

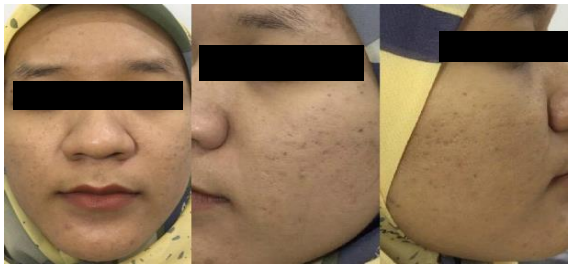

Figure 3 After first session (combination treatment of subcision and fractional CO2 laser).

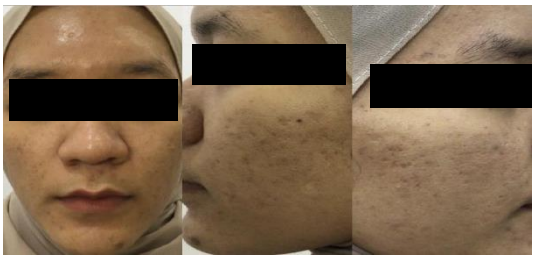

Figure 4 Last session (fractional CO2 laser only).

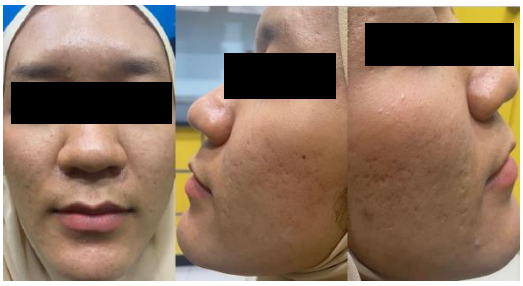

Figure 5 After last session.

Discussion

In this study, we combined two types of scar treatment which is subcision and ablative fractional laser [17,18]. The subcision procedure was conducted using cannula instead of needle as there were multiple studies done and proven that the outcome was both effective and economic, but cannula method offers less side effect and complications such as ecchymoses, hypertrophic scar, hyperpigmentation, redness and nodule formation. However, there's limitation as shown in the result that the acne scars that show improvement are mostly the rolling type as subcision and fractional laser was the main treatment done in this patient. She still has the ice pick scars which are yet to be resolved. Thus, there are many other options of treatment that can be added for this patient to combat the ice pick scar subsequently providing the best outcome for the patient.

Some of the other treatments that will work wonders on the ice pick scar includes chemical peels primarily TCA CROSS, microdermabrasion and also something more invasive which is punch excision. In addition to better outcomes, performing treatments together provides advantage to the patients. Combination

scar treatment can help to decrease total sessions needed, reduce the overall cost and provide more comfort during the process.

Conclusion

The proper choice of treatment modalities for acne scar remains a great challenge. According to our study, it has been proven that significant improvement can be achieved with combination treatment sessions that utilize a minimum of two or more of different types of atrophic scar treatments, either the same day or over a series of time.

References

1. Vempati A, Zhou C, Tam C, Khong J, Rubanowitz A, Tam K, Hazany S, Vasilev R, Hazany S. Subcision for atrophic acne scarring: a comprehensive review of surgical instruments and combinatorial treatments. Clinical, Cosmetic and Investigational Dermatology. 2023;125-134.
2. Gozali MV, Zhou B. Effective treatments of atrophic acne scars. The Journal of Clinical and Aesthetic Dermatology. 2015;8(5):33.
3. Fabbrocini G, Annunziata MC, D'arco V, De Vita V, Lodi G, Mauriello MC, Pastore F, Monfrecola G. Acne scars: pathogenesis, classification and treatment. Dermatology Research and Practice. 2010 ;893080.
4. Fife D. Practical evaluation and management of atrophic acne scars: tips for the general dermatologist. The Journal of Clinical and Aesthetic Dermatology. 2011;4(8): 50-57.
5. Orentreich DS, Orentreich N. Subcutaneous incisionless (subcision) surgery for the correction of depressed scars and wrinkles. Dermatologic Surgery. 1995;21(6):543-549.
6. Ebrahim HM, Artima AY, Elardi A, Mohamed Morsi H. Clinical and histopathological evaluation of different tools for the subcision of atrophic acne scars. Journal of Cosmetic Dermatology. 2022;21(3):1127-1134.
7. Jacob CI, Dover JS, Kaminer MS. Acne scarring: a classification system and review of treatment options. Journal of the American Academy of Dermatology. 2001;45(1):109-117.
8. Petrov A, Pljakovska V. Fractional carbon dioxide laser in treatment of acne scars. Open Access Macedonian Journal of Medical Sciences. 2016;4(1): 38-42.
9. Ochi H, Tan L, Tan WP, Goh CL. Treatment of facial acne scarring with fractional carbon dioxide laser in Asians, a retrospective analysis of efficacy and complications. Dermatologic Surgery. 2017;43(9):1137-1143.
10. Alexiades-Armenakas MR, Dover JS, Arndt KA. Fractional laser skin resurfacing. Journal of Drugs in Dermatology. 2012;11(11):1274-1287.
11. Chapas AM, Brightman L, Sukal S, Hale E, Daniel D, Bernstein LJ, Geronemus RG. Successful treatment of acneiform scarring with CO2 ablative fractional resurfacing. Lasers in Surgery and Medicine. 2008;40(6):381-6.
12. Thiboutot D, Gollnick H, Bettoli V, Dréno B, Kang S, Leyden JJ, Shalita AR, Lozada VT, Berson D, Finlay A, Goh CL. New insights into the management of acne: an update from the Global Alliance to Improve Outcomes in Acne group. Journal of the American Academy of Dermatology. 2009;60(5):S1-50.
13. Gupta A, Kaur M, Patra S, Khunger N, Gupta S. Evidence-based surgical management of post-acne scarring in skin of color. Journal of Cutaneous and Aesthetic Surgery. 2020;13(2):124-141.
14. AlGhamdi KM, AlEnazi MM. Versatile punch surgery. Journal of Cutaneous Medicine and Surgery. 2011;15(2):87-96.
15. Lee JB, Chung WG, Kwahck H, Lee KH. Focal treatment of acne scars with trichloroacetic acid: chemical reconstruction of skin scars method. Dermatologic Surgery. 2002;28(11):1017-1021.

16. Monheit GD, Chastain MA. Chemical Peels. Facial Plastic Surgery Clinics of North America. 2001;9(2):239-255.
17. Anupama YG, Wahab AJ. Effectiveness of CO2 laser with subcision in patients with acne scars. Journal of Cosmetic and Laser Therapy. 2016;18(7):367-371.
18. Sardana K, Garg VK, Arora P, Khurana N. Histological validity and clinical evidence for use of fractional lasers for acne scars. Journal of Cutaneous and Aesthetic Surgery. 2012;5(2):75-90.