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Effectiveness of Using 1% Diclofenac Gel and 20% Azelaic Acid Cream for Melasma: A Single-Blind, Placebo-Controlled, Split-Face Study

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Background: Non-steroidal anti-inflammatory drugs *that* inhibit the mediator of UV-induce*d* melanogenesis(1-6) may be another alternate option for melasma as were azelaic acid.

Objectives*: We conducted an evaluator-blind, placebo-controlled, split-face parallel group study to compare the effectiveness of 1% diclofenac gel with 20% azelaic acid cream and with placebo(moisturizer).*

Method: *36 participants with bilateral facial melasma were randomized into 3 groups: Group A, diclofenac compared to moisturizer; Group B, azelaic acid compared to moisturizer; Group C, diclofenac compared to azelaic acid. Interventions were randomized and applied to each side of the face twice daily. Sunscreens (SPF50, PA+++) were daily applied to the entire face. Primary outcomes were modified Melasma Area and Severity Index (MASI). Data were collected every 4 weeks for 12 weeks. The intention-to-treat proportions and per-protocol proportions were analyzed using paired* ***t****-test and repeated measures ANOVA.*

Results: *Modified MASI scores showed a significant decrease in diclofenac and azelaic compared to moisturizer (p= 0.041 VS P=0.017) and an insignificant difference in diclofenac compared to azelaic acid (p=0.287). Patient global satisfaction index were higher in diclofenac and azelaic compared to moisturizer (p=0.03 and p=0.05) but no difference while comparing diclofenac to azelaic (p=0.39). No difference of melanin and erythema index was significantly detected while comparing within groups. Irritations were observed in diclofenac (29%), azelaic (57%), and moisturizer (23%).*

Conclusion: *1% diclofenac is not different from 20% azelaic as an alternative treatment for melasma, more over, it is less irritating.*

Limitations*: Small sample size*

Disclosure: *No conflict of interest*

I. Introduction

Melasma is acquired bilateral recalcitrant hyperpigmentation, and it commonly manifests on the face. It impairs the quality of life by causing emotional illness and psychosocial burdens (7,8). Risk factors are genetic predispositions and hormonal influences. The pathogenesis of this pigmentary system dysfunction is multifactorial and can be triggered by UV light. Although the exact mechanism is unclear, sun protection is mandatory (9). To date, no standard treatments are available, but a reliable option is triple-combination therapy (TCT) (hydroquinone (HQ) 4%, tretinoin 0.05%, and fluocinolone acetonide 0.01%). However, the side effects of exogenous ochronosis, epidermal atrophy, and telangiectasia limit long-term use (9). Alternative options, including topical and oral medications, procedural therapies, and combination treatments, vary in their efficacy (9). Azelaic can decrease melanogenesis by inhibiting tyrosinase enzymes

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and reactive oxygen species. Currently Azelaic is widely used off-label in melasma treatments (9-11). Local irritation is a common problem (13-15), although many clinical trials favor Azelaic's efficacy (10,12).

There is a hypothesis about UV-inducing chronic inflammation. The major sources of the pro-inflammatory mediators are keratinocytes and epidermal melanocytes (16,17). Rodríguez, et al., (2015), states that there is more COX2 (cyclooxygenase-2) expressed in skin with melasma versus healthy skin (18). An important product of COX2 is prostaglandin E2 (PGE2), which stimulates the receptors on melanocytes, resulting in the production of cyclic adenosine monophosphate (cAMP). cAMP is the critical signaling mediator for melanocyte proliferation and melanogenesis (1-3). *In vitro* studies in murine melanoma cells demonstrated that nonsteroidal anti-inflammatory drugs (NSAIDs) can inhibit the α-Melanocyte stimulating hormone (α-MSH), and inhibit melanin synthesis and tyrosinase expression (4,5). Other studies show that topical NSAIDs can reduce skin darkening and erythema from UVA and UVB (6). 1% diclofenac gel is a well known non-selective COX(cyclooxygenase) inhibitor approved for pain relief in osteoarthritis (19).

1% diclofenac gel may inhibit UV-induced melanogenesis and may be useful in treating melasma. The purpose is to determine the effectiveness of 1% diclofenac gel, compared with 20% azelaic acid cream, and compared with placebo (moisturizer)in treating melasma.

II. Materials and Methods

Study Design

We conducted a pilot study (evaluator-blind, placebo-controlled, and split-face parallel) to compare the effectiveness of 1% diclofenac gel and 20% azelaic acid cream versus a placebo (moisturizer). Our study was conducted from January to June 2017 at the Institute of Dermatology, in Bangkok, Thailand. An institutional board approved the study, and all patients were given written informed consent materials.

Participants

The inclusion criteria were: males and females between 20-65 years old, with bilateral symmetrical melasma. The exclusion criteria were: pregnant or breast-feeding women, people with active facial acne, eczema, pigmentary, and/or endocrinopathies disorders. Patients who used oral contraceptive pills, whitening agents, and topical cosmetic depigmenting agents within 2 weeks of the study, or who had depigmentation procedures within 4 weeks of the study, were also excluded. No other melasma treatments were permitted during the study.

Data Collection

The random allocation software (20) allocated patients into 6 trial groups: 1. diclofenac, left versus moisturizer, right, 2. diclofenac, right versus moisturizer, left, 3. azeleic, left versus moisturizer, right, 4. azeleic, right versus moisturizer, left, 5. diclofenac, left versus azeleic, right, and 6. diclofenac, right versus azeleic, left. "Right" and "left" refers to the sides of the face. The dermatology resident (not involved in this trial) performed the allocation concealment. Interventions were categorized into three groups (A, B and C), where **Group A** represents diclofenac versus moisturizer, **Group B** represents azelaic acid versus moisturizer, and **Group C** represents diclofenac versus azelaic acid **(Figure 1**).

The interventions on the left side of the face were inserted into green cartridges and the opposite interventions were inserted into orange cartridges, thus blinding the patients. All interventions were applied to each side of the face twice daily, followed by broad-spectrum sunscreen (SPF 50, PA+++) applied once daily to the entire face. All interventions were applied to the face for 12 weeks. During four follow-up visits (baseline, Weeks 4, 8, and 12), the patients were assessed for endpoints, including the modified MASI score, the melanin index, and the erythema index. The patient Global Satisfaction Index (GSI) was collected at Week 12. Compliance was evaluated by weighing the cartridges at each visit via digital scales.

Endpoints

The primary endpoint was the modified MASI score (21), which was subjectively evaluated from the photographs. The scoring was performed by two blinded evaluators who were board certified dermatologists. The photography was performed using a VISIA-CR system and repeat measurements were held in a fixed position. We used the Wood's Light Mode (UV) of the camera to distinguish between epidermal and dermal pigmentation.

Secondary endpoints were GSIs, which subjectively scored the melasma improvements. At Week 12, patients were asked to decide which side showed more improvement. The degrees of improvement were: 0=No Change, 1=Very Slight Improvement, 2=Mild Improvement, 3=Moderate improvement, and 4=Marked Improvement.

Other secondary endpoints were degrees of pigmentation, redness, the melanin index, and the erythema index. They were objectively measured from both sides of the face (sternal notch included as a control site) every visit, using a narrowband reflectance spectrophotometer, Mexameter (Courage-Khazaka 18). No skin care products were applied to the measured sites at least 45 minutes prior to the measurements. All measuring was done at a temperature of 20±2°C and a relative humidity of 50% at the same time each visit to avoid diurnal skin changes.

Side effects, including redness, irritation, and itchiness were monitored by history and physical examination at each visit, and rated on a scale of 0 to 3, where 0=none, 1=mild, 2=moderate, and 3=severe. Patients were removed from the study if they reported severe local or adverse reactions post-intervention. Plans were made to terminate the study if severe adverse reactions occurred in more than 50% of interventions.

Statistical Analysis

This study analyzed both intention-to-treat and per-protocol populations. There were no interim analyses or stopping rules. The modified MASI score, melanin index, erythema index, and GSI were analyzed using a paired t-test and repeated measures ANOVA at Weeks 4, 8 and 12. All tests were two-sided and the critical values for efficacy endpoints were 0.05 – statistically significant effects. Inter-rater agreement was analyzed using Cronbach's alpha (22), with acceptable values ranging from 0.70 to 0.90 (23). All statistical analyses were performed using IBM SPSS (Version 22) and STATA14 software.

III. Results

Population

Eighty-four people were screened and 36 were enrolled according to the above criteria. Thirty-six patients were randomized into three separate treatment groups with 12 patients per group. Only one patient in Group A was lost at week 4 because of scheduling difficulties. Patients in Group B and C who could participate throughout the entire study are in **Figure 1.** Demographic data is in **Table 1.**

The mean age of the patients (six percent male and 83% female) was 45.72±9.28. Most had Fitzpatrick skin types III and IV, and all had mixed-type melasma with a mean duration of 6.43±8.65 years, mainly caused by sun exposure (66.7%).

Table 1 Demographic data

	Mean ± SD. or n (%)	Median [min, max]
Age	45.72 ± 9.28	46 [27, 64]
Male	6(16.7%)	
Female	30(83.33%)	
Fitzpatrick skin type	30(83.3%)	
III	6(16.7%)	
IV		
Underlying disease		
	(19.4%)	
Dyspepsia	2(5.%)	
Hypertension	2 (5.6%)	
Allergy	1 (2.8%)	
MIgraine	1 (2.8%)	
Hepatitis C carrier	1 (2.8%)	
Duration of melasma	6.43 ± 8.65	4 [0.42, 50]
Background treatment		
Hydroquinone	6 (16.7%)	
Steoids	5 (13.9%)	
Azelaic	2(6.95%)	
Retinoid	2(6.95%)	
Never treated	22 (61.1%)	
Familial melasma	10 (27.8%)	
Precipitating factor		
Sun exposures	24 (66.7%)	
Contraceptive pills	3 (8.3%)	
Pregnancy	4 (11.1%)	
Unknown	5 (13.9%)	
Type of melasma		
Mix tyoe	36(100%)	

Diclofenac Versus Moisturizer (Group A)

The modified MASI score in **Table 2** was acceptable according to agreement from two evaluators. The reliability is in **Table 3**. The baseline-modified MASI showed insignificant differences in both sides of the face (P >.05). Although improvement was seen at Week 4, no statistically significant differences were seen between the diclofenac and moisturizer sides, as per intention-to-treat and per-protocol proportions (P>0.05). At Week

12, the modified MASI score rose significantly in the moisturizer sides versus the diclofenac sides per as intention-to-treat proportions (p=0.041). Themelanin and erythema indexes were reported in **Tables 4** and **5**. The melanin index showed insignificant differences for both sides as per intention-to treat and per-protocol proportions (P>.05) from baseline to the end of Week 12. The GSI results significantly favored diclofenac versus moisturizer (P=0.031).

Table 2 Modified MASI score

(per-protocol)	**Moisturizer (M)**		**Diclofenac (D)**		**Azeleic (A)**		***p-value*** [(t)]					
	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD	n	**C vs. D**	n	**C vs. A**	n	**D vs. A**
Baseline	24	2.74 ± 1.5	24	2.61 ± 1.13	24	2.81 ± 1.34	12	0.837	12	0.804	12	0.668
(Baseline)	*20*	*2.55 ± 1.54*	*17*	*2.34 ± 1.11*	*21*	*2.75 ± 1.38*	*8*	*0.106*	*11*	*0.804*	*9*	*0.853*
4 weeks	22	2.54 ± 1.48	21	2.35 ± 1.27	23	2.62 ± 1.36	10	0.93	12	0.395	11	0.633
(4 weeks)	*20*	*2.4 ± 1.45*	*17*	*2.19 ± 1.29*	*21*	*2.64 ± 1.41*	*8*	*0.154*	*11*	*0.395*	*9*	*0.343*
8 weeks	20	2.34 ± 1.26	18	2.36 ± 1.31	22	2.62 ± 1.53	9	0.267	12	0.479	10	0.852
(8 weeks)	*20*	*2.34 ± 1.26*	*17*	*2.22 ± 1.19*	*21*	*2.52 ± 1.49*	*8*	*0.267*	*11*	*0.479*	*9*	*0.824*
12 weeks	23	2.84 ± 1.5	23	2.4 ± 1.21	24	2.6 ± 1.34	12	0.041 *	12	0.017 *	12	0.197
(12 weeks)	*20*	*2.59 ± 1.36*	*17*	*2.08 ± 1.06*	*21*	*2.46 ± 1.27*	*8*	*0.259*	*11*	*0.017 **	*9*	*0.287*
p-value [(A)]		*(per-protocol)*		*(per-protocol)*		*(per-protocol)*						
4 weeks	0.077	*0.079*	0.138	*0.251*	0.397	*0.504*						
8 weeks	0.167	*0.167*	0.732	*0.494*	0.319	*0.232*						
12 weeks	0.61	*0.844*	0.17	*0.137*	0.256	*0.115*						
Repeated ANOVA	0.272	*0.272*	0.293	*0.293*	0.231	*0.231*						

Values presented as mean ± SD. P-value corresponds to[(t)]Paired t test and [(A)]Repeated ANOVA test

Figure2 Modified MASI score

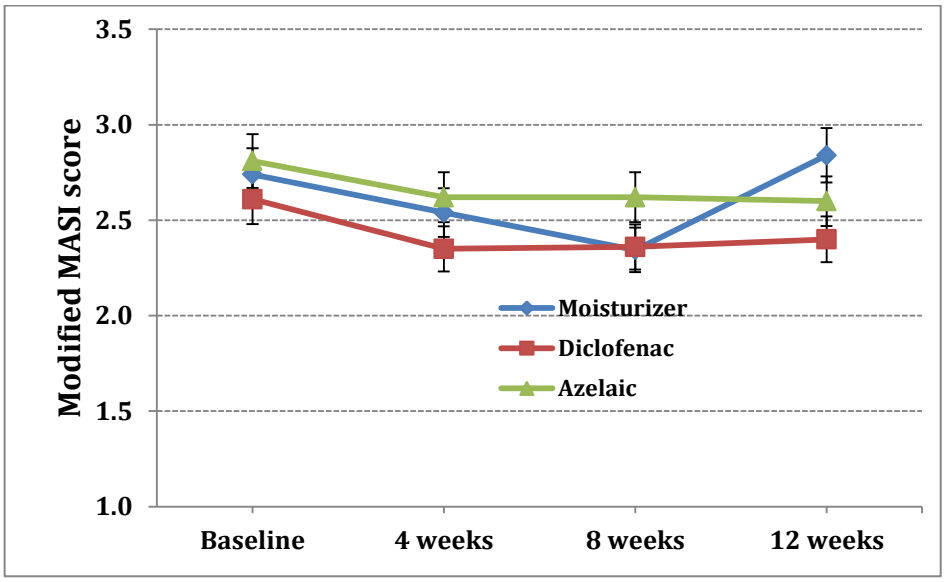

Fig 1 Modified MASI score

Table3 Inter-rater reliabilities

Cronbach's Alpha	Left(95%CI)	Right(95%CI)
Forehead area	0.755 (0.657, 0.825)	0.783 (0.696, 0.845)
Forehead darkness	0.726 (0.616, 0.804)	0.83 (0.762, 0.879)
Malar area	0.721 (0.609, 0.801)	0.789 (0.705, 0.85)
Malar darkness	0.517 (0.323, 0.656)	0.633 (0.486, 0.738)
Chin area	0.335 (0.068, 0.525)	0.29 (0.005, 0.493)
Chin darkness	0.469 (0.256, 0.621)	0.432 (0.204, 0.595)
Modified MASI	0.727 (0.618, 0.806)	0.798 (0.718, 0.856)

Azelaic Acid Versus Moisturizer (Group B)

The modified MASI score (**Table 2**) from baseline to Week 8 indicated insignificant differences between both sides (P>.05). However, azelaic sides were significantly superior to moisturizer sides proportions (0.017 versus 0.017).

The melanin index and erythema indexes were reported in **Tables 4 and 5**, from baseline to the end of Week 12. The melanin index indicated insignificant differences for both sides as per intention-to treat and per-protocol proportions (P>.05) from the baseline to the end of Week 12. The patient GSI results significantly favored azelaic acid over moisturizer (P=0.046).

Diclofenac Versus Azelaic Acid (Group C)

The modified MASI score, melanin index, erythema index, and patient GSI indicated insignificant differences between both sides by intention-to treat and per-protocol proportions (P>.05) from baseline to Week 12 (**Tables 2, 4, 5, and 6**).

Table 4.1 The melanin index comparing with-in interventions

Melanin index	**Moisturizer (M)**		**Diclofenac (D)**		**Azelaic (A)**		**Sternal notch**	
(per-protocol)	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD
Baseline	24	324.21 ± 66.72	24	312.83 ± 55.71	24	304.13 ± 83.17	36	252.39 ± 76.04
(Baseline)	*20*	*320.7 ± 69.77*	*20*	*282.67 ± 40.95*	*22*	*298.15 ± 80.52*		
4 weeks	23	322.3 ± 61.76	21	306.41 ± 66.1	23	310.09 ± 72.14	34	245.47 ± 63.55
(4 weeks)	*20*	*323.45 ± 62.1*	*20*	*290.17 ± 60.88*	*22*	*307.9 ± 72.53*		
8 weeks	20	308.74 ± 52.19	20	286.72 ± 53.5	22	313.57 ± 85.03	31	241.13 ± 53.57
(8 weeks)	*20*	*316.05 ± 66.01*	*20*	*296.11 ± 56.51*	*22*	*317 ± 87.96*		
12 weeks	23	327.78 ± 56.6	22	330.35 ± 60.81	23	328.13 ± 86.36	34	265.34 ± 69.33
(12 weeks)	*20*	*320.1 ± 63.54*	*20*	*310.56 ± 52.2*	*22*	*328.5 ± 95.74*		
p-value [(A)]		*per-protocol*		*per-protocol*		*per-protocol*		
4 weeks	0.903	*0.762*	0.692	*0.485*	0.453	*0.239*		0.759
8 weeks	0.262	*0.673*	0.724	*0.261*	0.068	*0.046**		0.5
12 weeks	0.462	*0.947*	0.057	*0.020**	0.055	*0.016**		0.362
Repeated ANOVA	0.407	*0.795*	0.056	*0.098*	0.05	*0.021**		*0.251*

Table 4.2 The melanin index comparing between interventions

Melanin index	***p-value*[(t)]**					
(per-protocol)	n	**M vs. D**	**n**	**M vs. A**	**n**	**D vs. A**
Baseline	12	0.775	12	0.51	12	0.979
(Baseline)	*9*	*0.307*	*11*	*0.192*	*11*	*0.579*
4 weeks	10	0.08	12	0.954	11	0.793
(4 weeks)	*9*	*0.197*	*11*	*0.453*	*11*	*0.965*
8 weeks	9	0.229	11	0.201	11	0.918
(8 weeks)	*9*	*0.128*	*11*	*0.144*	*11*	*0.574*
12 weeks	11	0.446	12	0.383	11	0.698
(12 weeks)	*9*	*0.597*	*11*	*0.469*	*11*	*0.699*

Values presented as mean ± SD. P-value corresponds to [(t)] Paired t test and [(A)]Repeated ANOVA test

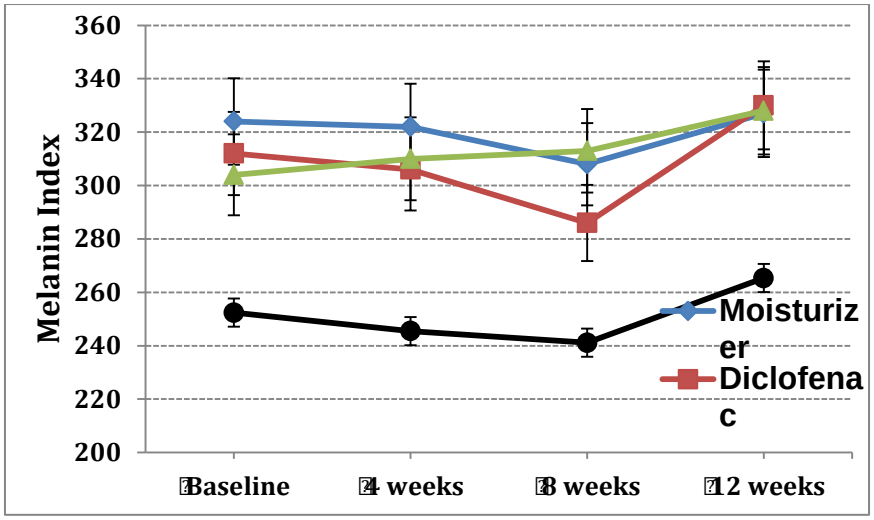

Fig 3 Melanin index

Table 5.1 The erythema index comparing with-in interventions

Erythema index	Moisturizer (M)		Diclofenac (D)		Azeleic (A)		Sternal notch	
(per-protocol)	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD		
Baseline	24	328 ± 59.7	24	326.13 ± 57.66	24	328.46 ± 63.78	36	346.61 ± 66.86
(Baseline)	*20*	*320.55 ± 60.27*	*18*	*309.06 ± 54.1*	*20*	*321.05 ± 64.49*		
4 weeks	23	335.26 ± 61.7	22	321.36 ± 76.61	23	340.43 ± 61.55	34	339.68 ± 59.04
(4 weeks)	*20*	*334.7 ± 62.71*	*18*	*311.67 ± 75.91*	*20*	*333.7 ± 59.85*		
8 weeks	20	327.8 ± 66.57	20	328.1 ± 62.14	22	340.05 ± 55.98	31	334.33 ± 71.83
(8 weeks)	*20*	*327.8 ± 66.57*	*18*	*327.17 ± 65.35*	*20*	*336.2 ± 56.68*		
12 weeks	23	331.26 ± 63.54	23	334.91 ± 57.27	23	343.09 ± 72.42	34	352.14 ± 68.07
(12 weeks)	*20*	*325.85 ± 58.67*	*18*	*321.78 ± 54.02*	*20*	*343.05 ± 75.21*		
p-value [(A)]		*per-protocol*		*per-protocol*		*per-protocol*		
4 weeks	0.315	*0.126*	0.896	*0.827*	0.116	*0.135*		0.543
8 weeks	0.475	*0.475*	0.201	*0.132*	0.082	*0.118*		0.593
12 weeks	0.616	*0.487*	0.261	*0.261*	0.072	*0.046**		0.455
Repeated ANOVA	0.476	*0.476*	0.266	*0.266*	0.124	*0.124*		0.676

Table 5.2 the erythema index comparing between interventions

Erythema index		*p-value*$^{(t)}$				
(per-protocol)		**M vs. D**		**M vs. A**		**D vs. A**
Baseline	12	0.512	12	0.325	12	0.462
(Baseline)	*9*	*0.528*	*11*	*0.383*	*11*	*0.428*
4 weeks	10	0.233	12	0.491	11	0.801
(4 weeks)	*9*	*0.377*	*11*	*0.476*	*11*	*0.727*
8 weeks	9	0.576	11	0.926	11	0.824
(8 weeks)	*9*	*0.576*	*11*	*0.926*	*11*	*0.36*
12 weeks	11	0.422	12	0.813	11	0.779
(12 weeks)	*9*	*0.374*	*11*	*0.742*	*11*	*0.767*

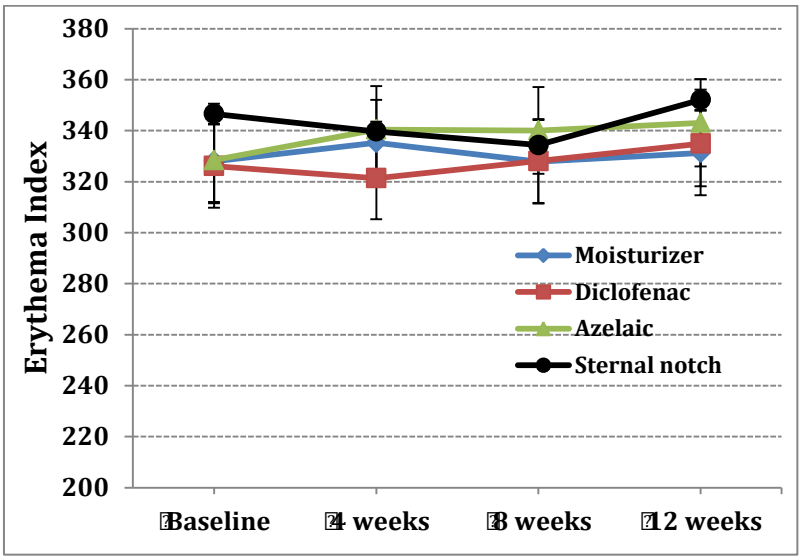

Fig 4 Erythema index

Table 6 Global satisfaction index

	Moisturizer (M)		**Diclofenac (D)**		**Azelaic (A)**	*p-value*$^{(t)}$		
	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	**M vs. D**	**M vs. A**	**D vs. A**
Score	23	2.09 ± 1	23	3.13 ± 0.81	24	2.79 ± 0.93	0.031*	0.046*	0.394

Values presented as mean ± SD. P-value corresponds to $^{(t)}$ Paired t test.

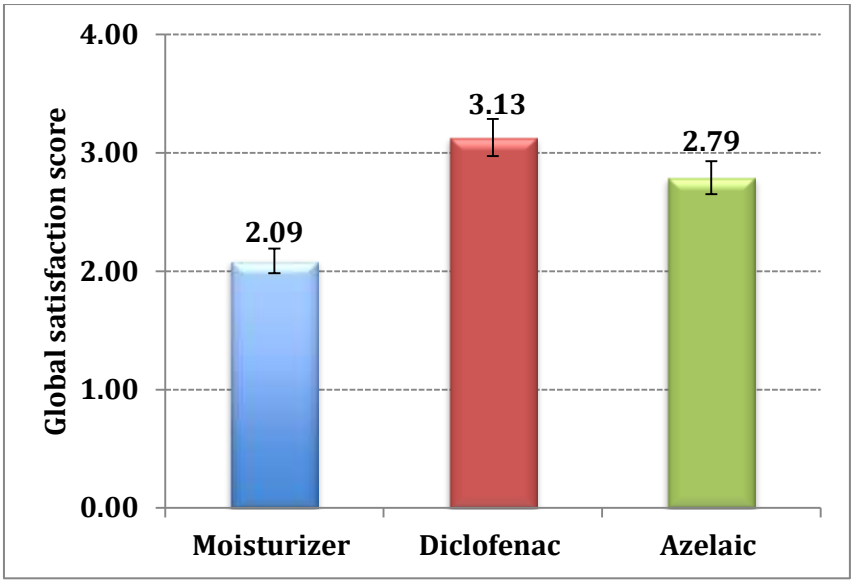

Figure 5 Global satisfaction score

Comparing Diclofenac, Azelaic and Moisturizer Sides from Baseline to Week 12

The mean modified MASI score (**Table 2 and Figure 2**), from baseline to Week 8, was reduced in all interventions then the scores for the diclofenac and azelaic sides were stabilized via the intention-to-treat analysis. Notably, the modified MASI score for the per-protocol proportion showed continuous improvement from baseline to Week 12 in the diclofenac and azelaic sides. The mean modified MASI scores for the moisturizer increased as follows: Week 8 intention-to-treat proportions: 2.34±1.26, Week 12: 2.84±1.5, and per-protocol proportions, Week 8: 2.34±1.26, Week 12: 2.59±1.36. However, no statistical significance was detected. Repeated ANOVA statistical tests of all interventions, in both intention-to-treat and per-protocol proportions, showed no significant differences of the modified MASI scores throughout the study.

The melanin index (**Tables 4.1, 4.2, and Figure 3**) from intention-to-treat proportions decreased from baseline to Week 8. It rose at Week 12 in all moisturizer, diclofenac, and azelaic sides. These results correlated to the control area at the sternal notch, which had no interventions. The intention-to-treat analysis showed no statistical differences in all treatment sides. Per-protocol analysis demonstrated that the melanin index in all sides increased. Detection was obvious at Weeks 8 and 12 in the azelaic sides (P=0.046 and P=0.016) and at Week 12 in the diclofenac sides (P=0.020).

The erythema indexes (**Table 5 and Figure 4**), showed no significant differences from baseline to Week 12 in intention-to-treat proportions for all the moisturizer, diclofenac, and azelaic sides, including the sternal notch area. However, per-protocol analysis demonstrated that the erythema index in azelaic sides rose significantly at Week 12 (P=0.046).

The GSI (**Table 6 and Figure 5**) was highest in the diclofenac sides (mean ± SD=3.13±0.81), followed by the azelaic sides (mean ± SD=2.79±0.93), and the moisturizer sides (mean ± SD=2.09±1).

Safety

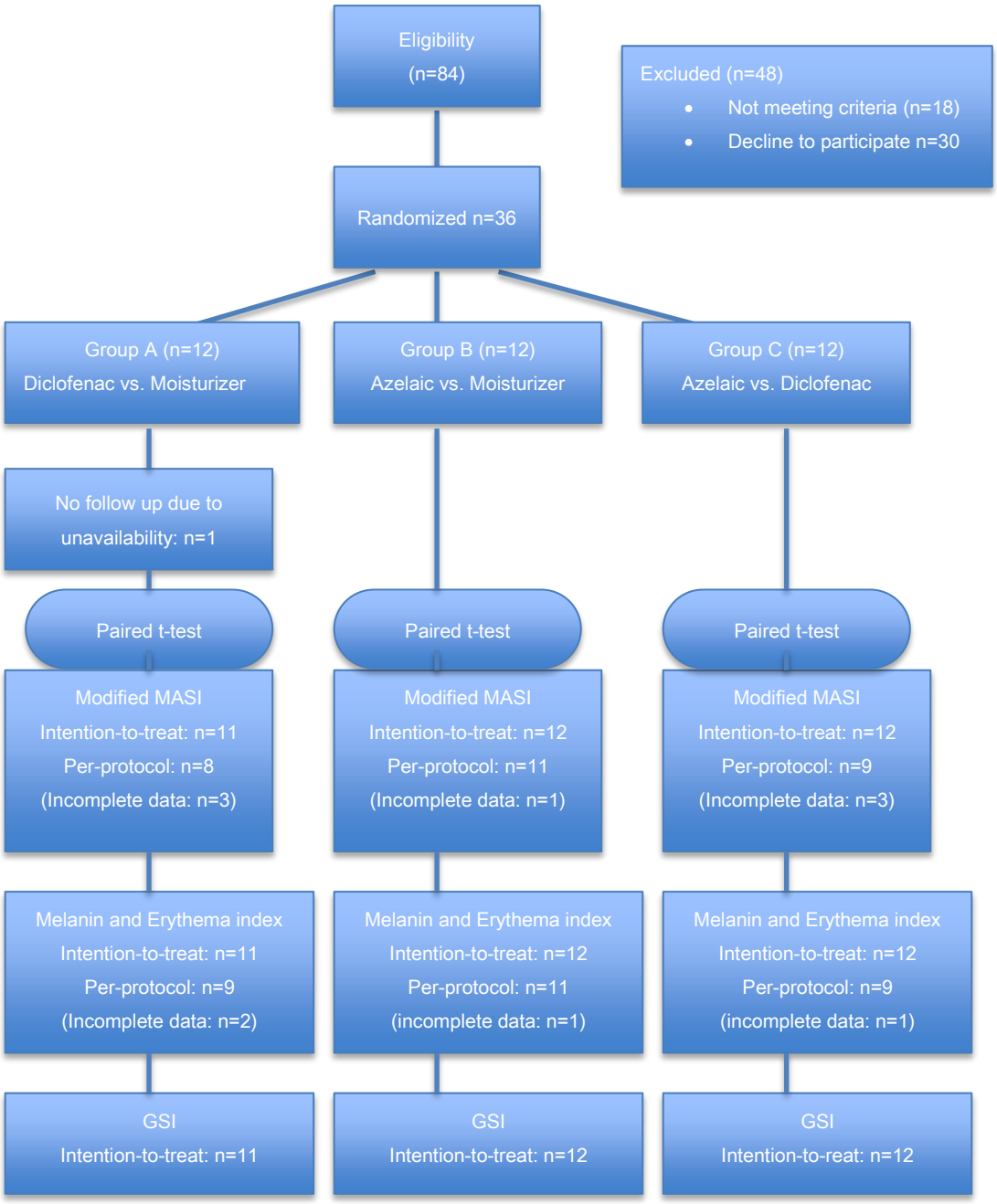

Figure 1, Flow Diagram

n = Number of Patients

No serious adverse events or systemic side effects were reported. Local reactions were observed, but were reported to be mild. At Weeks 4, 8, and 12, irritation **(Figure 6**) was highest in the azelaic side (52-57%), followed by thediclofenac (29-42%) and moisturizer sides (16-33%). Redness (**Figure 7**) was similar in the azelaic sides (10-20%) and the diclofenac sides (5-20%), but very low in the moisturizer sides (0-8%). Itchiness (**Figure 8**) was highest in the azelaic sides (50-60%) ,followed by the diclofenac (14-37%) and moisturizer sides (16-31%).

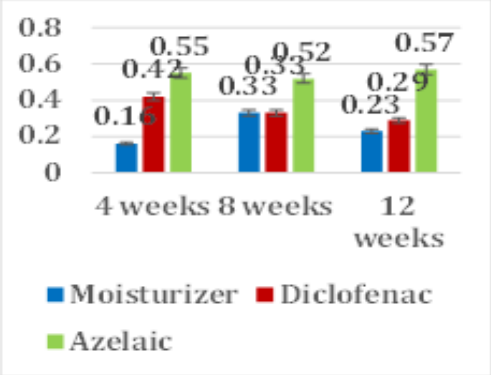

Figure. 6 Irritation

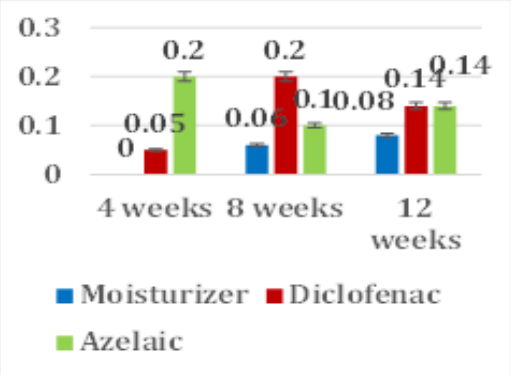

Figure 7 Redness

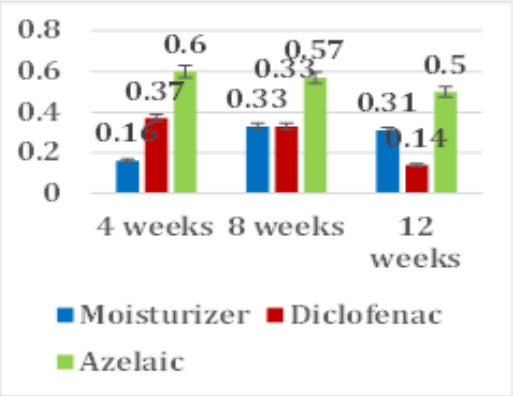

Figure 8

IV. Discussion

Our pilot study used three pairs (**Group**s **A, B and C**) and measured the same outcomes. The subjective outcomes of our project were modified MASI scores (primary outcome) and the GSI (secondary outcome). Objective outcomes were the melanin and erythema indexes.

In **Group A** at 12 weeks, we detected that diclofenac is superior to moisturizer via all subjective measurement methods. However, the erythema index did not show any difference between diclofenac and moisturizer. This can be explained by the use of sunscreen, which filters UVB-inducing erythema (24). The inhibition of COX by diclofenac resulted in the reduction of PGE2(3).

An *in vitro* study (2008) demonstrated that aspirin inhibited tytosinase expression in dose-dependent mechanisms, and could inhibit alpha-MSH-enhanced melanin synthesis in murine melanoma cells (4). Another *in vitro* study (2011) showed that diclofenac inhibited MSH-enhanced tyrosinase activity in a dose- dependent manner (5). Human studies reveal that topical NSAIDs inhibit UV-induced melanogenesis by photoprotective effects (6).

Our study shows that the combination of sunscreen with diclofenac is superior to the combination of sunscreen with moisturizer. This could be the additional photoprotective mechanism of diclofenac. **Group B** demonstrated that azeleic is superior to moisturizer by all subjective measurements. These results confirm the results of a previous clinical trial by Lowe, et al., which also compared 20% azeleic acid to vehicle to treat facial hyperpigmentation in darker skin.

Group C showed that diclofenac does not differ from azeleic by all objective and subjective measurements, and there was no difference in patient satisfaction via intention-to-treat and per protocol proportions. This is the first study where the efficacy of diclofenac with azelaic and moisturizer was compared, and it raised the possibility of a new potential antimelanotic agent candidate.

All interventions had no significant reduction of pigmentation, as measured by the modified MASI score. Notably, the melanin and erythema index of the treated area rose corresponding to the control area (sternal notch). Our study may have been affected by the approaching summer season, because both the melanin and erythema indexes were vulnerable to physical stimuli and the UV-induced response in a dose-dependent manner (25,26). The erythema indexes of azelaic rose from Weeks 4 to 12 and were obvious through per-protocol analysis. This may relate to the obvious local irritation, redness, and itchiness side effects reported by the patients for the azelaic side. These side effects were similar to a previous study by Lowe, et al., who reported obvious burning at Weeks 4 and 12 (14).

Local side effects of irritation, redness, and itchiness from 1% diclofenac were mild and transient. These correlate with a 2016 systematic review by Derry S., et al., where no systemic side effects were observed (19). Allergic sensitizations were not reported from all interventions.

The limitations of our study were small sample sizes and short observation periods. Additional observations during the off-treatment period could identify melasma relapse. Additionally, the unique scent and texture of diclofenac gel compared to azeleic cream may result in incomplete blinding and could lead to reporting biases.

V. Conclusion

Our study indicates that 1% diclofenac gel and 20% azeleic acid can be applied to melasma as an alternative treatment with favorable effects. However, large-scale, blinded RCTs, with a longer observation period, should be implemented before 1% diclofenac gel can be recommended as a therapeutic option.

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