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Microneedling with Ginkgo Biloba Solution plus Narrow Band Ultraviolet B Phototherapy in the Treatment of Non-Segmental Vitiligo: Comparative Intra-Individual Placebo Controlled Study

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Abstract: Introduction: Vitiligo is a common cutaneous disease characterized by depigmented skin patches that may become a source of embracement for affected individuals. One of its popular lines of treatment is narrow band UVB that is widely used. Another line is microneedling that aims to induce a minimal superficial bleeding stimulating the releases of growth factor to start a healing cascade to restore normal structure. Although the etiology of vitiligo is not yet well understood, a biochemical theory was proposed suggesting an oxidative stress within the vitiliginous skin. Ginkgo biloba is plant-based medicine used as antioxidant in many specialties. These antioxidant properties can play an important role in protecting melanocytes from the oxidative stress and thus inhibit the progression of vitiligo. **Patients and study design:** A randomized clinical trial was performed on 20 vitiligo patients selected from those attending at Outpatient Clinic of Dermatology, Al-Azhar University Hospitals. All participants were subjected to full history taking and complete clinical. Those who had vitiligo that was stable at least in the last month prior to study beginning with ages ranging from 10 to 65 years were selected. For each participant, three similar patches were selected; first patch was exposed to NB-UVB, microneedling and ginkgo biloba solution; second patch was exposed to NB-UVB, microneedling and saline; third patch was exposed to NB-UVB only. All patches were treated for 12 weeks. Assessment of repigmentation was performed through three independent investigators. **Results:** The current study results revealed a significant increase in vitiligo among females than males. In addition, the positive family history was evident in minority of cases. It also found that the most common type of vitiligo is the widely spread type. The present work found a significant improvement in patches exposed to NB-UVB, microneedling and ginkgo biloba solution compared to NB-UVB and microneedling with saline or NB-UVB only. Furthermore, patients' satisfaction was significantly high in the first group compared with the two groups. It also revealed no significant difference concerning improvement between patches exposed to NB-UVB and microneedling with saline and patches exposed to NB-UVB only.

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1. Introduction

Vitiligo is a common incurable disease characterized by white depigmented skin patches. These patches may result in a psychological stress for those who are affected **(Iacovelli et al., 2019)**. Globally about 1- 3% of people are affected by vitiligo **(Kruger and Schallreuter, 2012).** It is classified into segmental, non-segmental and unclassifiable forms vitiligo **(Ezzedine et al., 2012).**

The etiology of vitiligo is not yet well understood. Many theories have been described such as neurological theory, auto-immune theory, viral theory and intrinsic theory. One of these theories is the biochemical theory that support the fact that oxidative stress can strike melanocytes and initiates their apoptosis **(Vrijman, 2019).**

The goal of vitiligo treatment is to prevent damage to melanocytes and stimulate their migration from surrounding skin and adnexal reservoirs. One of lines of treatment is narrow band UVB (311 nm) which is effective and safe therapeutic modality, treatment with narrow. Another line of treatment is microneedling that aims to induce a minimal superficial bleeding stimulating the releases of growth factor to start a healing cascade to restore normal structure **(Majid et al., 2014).**

Ginkgo biloba is derived from maidenhair tree. Ginkgo biloba has been used in China as a

traditional medicine for a range of conditions, including asthma, bronchitis, heart dysfunction, for at least 5000 years (**Lv et al., 2017).**

Ginkgo biloba is widely used in neurological and neuropsychiatric including dementia, Alzheimer, schizophrenia, multiple sclerosis and attention deficit hyperkinetic disorder (**Diamond and Mondragon, 2017). Wang et al. (2016)** reported that Ginkgo biloba extract has a cardio-protective effect against inflammatory reaction, oxidative stress and structural damage.

While Oxidative stress plays a major role in vitiligo, ginkgo biloba has antioxidant properties that inhibit the progression of vitiligo and also through its anxiolytic properties since psychological stress has been shown to exacerbate vitiligo (**Szczurko et al., 2011).**

Aim of the work

The aim of this study is to evaluate the effect of microneedling with ginkgo biloba solution on the outcome in non-segmental vitiligo during the sessions of narrow band ultraviolet B phototherapy.

2. Patients and Methods

Patients

This study is a randomized clinical trial included 20 patients suffering from vitiligo. These participants were selected from those attending at Outpatient Clinic of Dermatology, Al-Azhar University Hospitals.

Ethical approval from The Medical Research Ethics Committee was obtained. In addition, written consents were taken from all participants before enrollment in the study.

- **Inclusion criteria**

1. Patients having vitiligo which was stable at least in the last month prior to study beginning.
2. Ages ranging from 10 to 65 years.
3. Both sexes were included.

- **Exclusion criteria**

1. Acute and chronic diseases such as anemia, kidney and liver disease, diabetes, ischemic heart disease, oncological diseases, etc.
2. Mentally or psychologically disoriented patients.
3. Presence of active infection.
4. Refusal of participation.

Materials

1. Ginkgo biloba

Ginkgo biloba was obtained in the form of ampoules, each one (2 ml) contains 4% ginkgo biloba solution® (mccosmetics company, Barcelona, Spain).

2. Normal saline 0.9%

Normal saline (sodium chloride 0.9%) was obtained in the form of 500 ml containers, each container contains 0.9 gm sodium chloride dissolved it 100 ml injection water (El-Fath for Drug and Cosmetics Industries, Borg El-Arb, Egypt).

3. Prilocaine cream 5%

EMLA® cream 5% was obtained in the form 5 gm tubes, each one contains prilocaine/lidocaine (Astra Zeneca, Sweden).

Methods

All members of the study will be subjected to the following:

- **Complete history taking** including age, sex, marital status, address, contact information; onset, course and duration of the present condition, medical history of any associated systemic or dermatologic diseases, family history of vitiligo and previous treatment for it.
- **Dermatological examination** including detection of lesion site, vitiligo type, site and size of the lesions and skin phototype.
- **Three vitiliginous patches** of nearly the same size were randomly selected within the same individual and **each patch received different treatment for 12 weeks**:
  - **The first patch (U)** was exposed to two sessions of NB-UVB weekly with a starting dose of 0.2 J/cm^2 and increasing by 20 % every session till minimal erythema dose was achieved. *The NB-UVB source UV series equipment, Daavlin 7 series (USA), fig. VII with a spectrum of 280-320 nm.*
  - **The second patch (UDS)**: the same as the first patch except that after one of the two weekly sessions, the patch was exposed to skin microneedling using automatic needling device *(Dr. Pen Auto Microneedle System Ultima-A1, Fig. VIII)* as following

1- Topical anesthetic gel (EMLA 5% cream) was applied to skin under occlusion for 30 minutes.

2- Skin cleaning with ethyl alcohol.

3- A dermapen -set with a needle depth at 0.5 to 1 mm- is applied in both horizontal and vertical lines till the affected area reach pin point bleeding.

4- 0.5 to 1 ml of normal saline 0.9% was applied topically to the bleeding area, rubbed and left under occlusion for 30 minutes.

- **The third patch (UDG)**: the same as the second patch except that ginkgo biloba solution was used instead of normal saline after microneedling took place.

Evaluation of the therapeutic efficacy

1- Clinical assessment

Serial photographs using digital camera (BenQ DC C1030, 10.0 Mega Pixels) with the same resolution and lighting features were taken before the treatment, every session and at the end of treatment period then clinical evaluation of the degree of repigmentation was done by two independent blinded

investigators for the three patches and scores were given as following:

- Excellent improvement: >75% repigmentation.
- Good improvement: 50-75% repigmentation.
- Fair improvement: 25-50% repigmentation.
- Poor improvement: <25% repigmentation.

2- Safety assessment

The patients were informed to report any complications as; erythema, pain, ulceration, burning sensation, ecchymosis, infection, post-inflammatory hyperpigmentation or any allergic manifestations.

3- Pain assessment during session

During each session, participant's pain was assessed according to the visual analogue scale (Fig. IX) where zero means no pain at all and 100 is the worst pain.

Statistical analysis of the data (Dean, 2006).

Data entry and statistical analysis were performed using SPSS (Statistical Package of Social Sciences) version 21. Categorical data were expressed in number and percentage. Continuous normally distributed data were expressed in mean and standard deviation while none-normally distributed data were expressed in median and range. The quantitative data were examined by Kolmogrov Smirnov test for normality of data.

Comparing of categorical data was done using chi square test or fisher exact test whenever appropriate. Statistical significance was considered when probability (P) value was less than or equal to 0.05.

3. Results

Table (1) shows the demographic data for included participants. **As regard age,** the mean age of studied patients was 29.8 ± 18.5 years with minimum age of 11 years and maximum age of 60 years. **As regard sex,** there were 6 males (30%) and 14 females (70%) in the studied patients. **as regard family history,** there were 18 patients (90%) of negative family history and 2 patients (10%) of positive family history.

Table (1): Demographic data for included participants

Demographic data		Studied patients (N = 20)	
Age (years)	Mean ±SD	29.8 ± 18.5	
	Min - Max	11 – 60	
Sex	Male	6	30%
	Female	14	70%
Family History	Negative	18	90%
	Positive	2	10%

Table (2): Description of clinical data in studied patients

Clinical data		Studied patients (N = 20)	
Duration of disease (years)	Mean ±SD	4.05 ± 2.4	
	Min - Max	1 – 9	
Skin type	III	15	75%
	IV	5	25%
Type of vitiligo	Acral	2	10%
	Wide spread	18	90%
Site of lesion	Arm	4	
	Face	2	
	Trunk	11	
	Hands	6	
	Leg	12	
	Foot	12	
	Elbow	2	
	Neck	2	
Previous treatment	UVB	20	
	Topical	18	
	Vitamins	4	
	systemic corticosteroids	2	
	Intra-lesional 5-fu	1	

Table (2) This table shows the clinical data in studied patients. **As regard duration of disease,** the mean duration of studied patients was 4.05 ± 2.4 years with minimum duration of 1 year and maximum duration of 9 years. **As regard skin type,** there were 15 patients (75%) of skin type III and 5 patients (25%) of skin type IV in the studied patients.

As regard type of vitiligo, there were 2 patients (10%) of Acral vitiligo and 18 patients (90%) of wide spread vitiligo. **As regard Site of lesion,** arm was affected in 4 patients; Face was affected in 2 patients, trunk was affected in 11 patients, hands were affected in 6 patients, Legs were affected in 12 patients, foot was affected in 12 patients, elbow was affected in 2 patients and neck was affected in 2 patients.

As regard previous treatment, UVB was used in all patients, topical treatment was used in 18 patients, vitamins were used in 4 patients, systemic corticosteroids were used in 2 patients and intra-lesional 5-fu was used in 1 patient.

Table (3) shows statistically significant difference **(p-value < 0.05)** between studied patches (UDG & UDS) as regard improvement.

Table (3): Comparison between studied patches (UDG & UDS) as regard improvement.

Improvement		UDG (N = 20)		UDS (N = 20)		Stat. test	P-value
Improvement	Poor	5	25%	10	50%	$X^2 = 8.83$	0.032 S
	Fair	3	15%	7	35%		
	Good	6	30%	1	5%		
	Excellent	6	30%	2	10%		

X^2: Chi-square test. S: p-value < 0.5 is considered significant.

Table (4) shows statistically significant difference **(p-value < 0.05)** between studied patches (UDG & U) as regard improvement.

Table (4): Comparison between studied patches (UDG & U) as regard improvement.

Improvement		UDG (N = 20)		U (N = 20)		Stat. test	P-value
Improvement	Poor	5	25%	16	80%	$X^2 = 12.33$	0.006 S
	Fair	3	15%	1	5%		
	Good	6	30%	2	10%		
	Excellent	6	30%	1	5%		

X^2: Chi-square test. S: p-value < 0.5 is considered significant.

Table (5) shows no statistical significant difference **(p-value > 0.05)** between studied patches (UDS & U) as regard improvement.

Table (5): Comparison between studied patches (UDS & U) as regard improvement.

Improvement		UDS (N = 20)		U (N = 20)		Stat. test	P-value
Improvement	Poor	10	50%	16	80%	$X^2 = 6.55$	0.088 NS
	Fair	7	35%	1	5%		
	Good	1	5%	2	10%		
	Excellent	2	10%	1	5%		

X^2: Chi-square test. NS: p-value > 0.5 is considered non-significant.

Table (6) shows Description of complications in studied patients. **As regard pain during session,** there were 15 patients (75%) of grade 10, 1 patient (5%) of grade 20, 2 patients (10%) of grade 30 and 2 patients (10%) of grade 40.

Table (7) shows statistically significant difference **(p-value < 0.05)** between studied patches (UDG & UDS) as regard satisfaction.

Table (6): Description of complications in studied patients.

Complications		Studied patients (N = 20)	
Pain during session	10	15	75%
	20	1	5%
	30	2	10%
	40	2	10%

Table (7): Comparison between studied patches (UDG & UDS) as regard satisfaction.

Improvement		UDG (N = 20)		UDS (N = 20)		Stat. test	P-value
Satisfaction	Poor	2	10%	8	40%	$X^2 = 10.3$	0.017 S
	Fair	3	15%	7	35%		
	Good	7	35%	2	10%		
	Excellent	8	40%	3	15%		

X^2: Chi-square test. S: p-value < 0.5 is considered significant.

Table (7) shows statistically significant difference **(p-value < 0.05)** between studied patches (UDG & U) as regard satisfaction.

Table (8): Comparison between studied patches (UDG & U) as regard satisfaction.

Improvement		UDG (N = 20)		U= (N = 20)		Stat. test	P-value
Satisfaction	Poor	2	10%	9	45%	$X^2 = 10.7$	0.014 S
	Fair	3	15%	6	30%		
	Good	7	35%	3	15%		
	Excellent	8	40%	2	10%		

X^2: Chi-square test. S: p-value < 0.5 is considered significant.

Table (9) shows no statistical significant difference **(p-value > 0.05)** between studied patches (UDS & U) as regard satisfaction.

Table (9): Comparison between studied patches (UDS & U) as regard satisfaction.

Improvement		UDS (N = 20)		U (N = 20)		Stat. test	P-value
Satisfaction	Poor	8	40%	9	45%	$X^2 = 0.53$	0.911 NS
	Fair	7	35%	6	30%		
	Good	2	10%	3	15%		
	Excellent	3	15%	2	10%		

X^2: Chi-square test. NS: p-value > 0.5 is considered non-significant.

4. Discussion

Vitiligo is a common incurable disease characterized by white depigmented skin patches. These patches may result in a psychological stress for those who are affected **(Iacovelli et al., 2019).**

Many theories have been described to justify the etiology of vitiligo. One of these theories was the oxidative stress within the vitiliginous skin caused by the progressive production of reactive oxygen species which disturb melanocytes metabolism with subsequent death and appearance of depigmented macules **(Vrijman, 2019).**

Narrow band UVB (NB-UVB) can be considered a first-line option for vitiligo. It acts mostly via inhibiting the destruction of melanocytes. Another line of treatment is microneedling that aims to induce a minimal superficial bleeding stimulating the releases of growth factor to start a healing cascade to restore normal structure **(Majid et al., 2014).**

Ginkgo biloba extracts are one of the still-used ancient plant-based product which possess antioxidant properties as they are rich in polyphenols and have the ability to elevate both enzymatic and non-enzymatic antioxidant defenses (**Oliveira et al., 2019).**

The current study is a randomized clinical trial performed on 20 vitiligo patients who were selected from those attending at Outpatient Clinic of Dermatology, Al-Azhar University Hospitals. For each participant, three similar patches were selected; 1st patch **(U)** was exposed to NB-UVB only,; 2nd patch **(UDS)** was exposed to NB-UVB, microneedling and saline; 3rd patch (**UDG**) was exposed to NB-UVB, microneedling and ginkgo biloba solution. Assessment of repigmentation was performed through three independent investigators.

The study aimed to evaluate the effect of both microneedling and ginkgo biloba solution on the outcome of NB-UVB sessions in non-segmental vitiligo.

In the present study, the mean age of studied patients was *29.8±18.5* years with predominance of females *(14/20; 70%)*. It also revealed that only 10% *(2/20)* of patients had a positive family history. These findings are concomitant with those of **Shajil et al. (2006)** who examined 424 vitiligo patients at Sir Sayajirao Gaikwad Medical College hospital Skin and Venereal OPD and a service hospital in Vadodara, India and declared that 61.56% (261/ 424) were females. However, they described that about 21.93% (61/424) had a positive family history. Also, the present study findings are in agreement with those of **Manolache and Benea (2007)** who performed a case control study at the dermatological department of Cetatea Histria Polyclinic, Bucharest between March 2001 and December 2005 and found that female predominance (14/17; 82%) was obvious in patients older than 21 years, while below that age both sex phenotypes were nearly equal (females represented 8/15; 53%). The previous authors also added that only 18% (6/32) of patients had a positive family history. **Kyriakis et al. (2009)** reported also that concerning patients between 20 and 60 years old, the prevalence of vitiligo in females is twice that of males. **Vora et al. (2014)** also reported that among vitiligo patients attending in outpatient department at Shree Krishna Hospital (SKH) and Matar camp, Gujarat, India from August 2011 to July 2012, females (578/1010; 57.3%) were more present than males. However the previous authors described a higher percentage of positive family history that reached 20.4 % *(204/1010)*.

In the present work, the mean duration of illness was 4.05±2.4 years (range from 1- 9 years) and the majority of patients had skin type III *(15/20; 75%)*. **Shajil et al. (2006)** reported a similar illness duration with their sample patients (*the average was 3.3 years*) as well as **Vora et al. (2014)** who reported that the duration of illness ranged from 1-5 years among their patients.

In the present work, widely-spread vitiligo was most frequent *(18/20; 90%)* with legs *(12/20)*, foot *(12/20)* and trunk *(11/20)* as the most frequently affected body parts. These findings are in agreement with **Vora et al. (2014)** who reported vitiligo vulgaris to be the most frequent (580/1010; 57.4%). However, they reported that the most frequently affected body parts were lower *(758/1010; 75.4%)* and upper limbs (688/1010; 68.3%).

In the present work, all patients- prior to the study- were already on NB-UVB *(20/20; 100%)* which is a very popular therapeutic method that is safe and effective with no serious side effects (**De Francesco et al., 2008**). In addition to NB-UVB, other lines of treatment were used such as topical treatment *(18/20; 90%)* and vitamins *(4/20; 20%)*.

In the present study, there was a statistically significant improvement in patches underwent microneedling with ginkgo biloba (**UDG**) when compared to both patches underwent microneedling with saline (**UDS**) (p=0.032) and patches underwent NB-UVB (**U**) only (p=0.006) as 30% (6/20) of **UDG** patches had an excellent improvement in comparison to 10% (2/20) of **UDS** patches in comparison to only 5% (1/20) of **U** patches. Furthermore, poor response reached 80% (16/20) of **U** patches compared to 50% (10/20) of **UDS** patches compared to 25% (5/20) of **UDG** patches. These results were perceived by patients themselves as **UDG** patches caused statistically significant satisfactory results compared with **UDS** (p=0.017) and **U** patches (p=0.014) for the same patient. However, there was no statistically significant difference regarding improvement (p=0.088) or patients satisfaction (p=0.911) between

both **UDS** and **U** patches. Such finding comes in favor of the oxidative stress theory in understating the etiology of vitiligo as addition of the well-known antioxidant ginkgo biloba solution to treatment with NB-UVB and microneedling showed a promising improvement when compared to either NB-UVB alone or with microneedling. Both **Xie et al. (2016)** and **He et al. (2017)** suggested also the same oxidative stress theory. They explained that oxidative stress depletes the nuclear factor E_2-related factor 2 (Nrf2) which is a critical transcription factor in protecting melanocytes with subsequent induction of autophagy.

The current study results agree with those of **Parsad et al. (2003)** who conducted a randomized clinical trial on 52 vitiligo patients by giving them ginkgo biloba at a dose of 40 mg orally 3 times daily for 6 month and found that *80 %* of patients showed cessation pf active disease and more than *40%* of them had repigmentation more than75%. Also, **Szczurko et al. (2011)** observed 12 vitiligo patients receiving 120 mg ginkgo biloba daily for 3 month and reported that all patients showed cessation of disease progression and the overall average repigmentation exceeded *15 %*. This good response was explained by **Cohen et al. (2015)** who described ginkgo biloba to have an anti-inflammatory properties that reduce the cyclooxygenase activity, decrease IL-8 and stimulate vascular endothelial growth factor release. **Gianfaldoni et al. (2018)** suggested the use of ginkgo biloba in treatment of vitiligo not only due having an anti-inflammatory but also an immunomodulatory properties. **Zhang et al. (2019)** added that gingko biloba has the ability to improve melanocyte viability, restore the activity of both superoxide dismutase and glutathione reductase enzymes and stimulate the production of Nrf2 in addition to its receptors.

These good results together with the easy topical application, minimal pain, no side effects and patient's satisfaction makes ginkgo biloba a promising treatment of vitiligo.

Conclusion

Combination of NB-UVB, microneedling and ginkgo biloba solution showed promising results in repigmentation of vitiliginous patches as well cessation of disease progression, especially that its application is easy, topical, minimal pain, no side effects and more patient's satisfaction.

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