

Combination effect of methotrexate with Narrowband Ultraviolet B (NB-UVB) phototherapy in psoriasis vulgaris patients in dermatology and venereology outpatient clinic Dr. Soetomo General Academic Hospital, Surabaya, Indonesia



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ABSTRACT

Background: Psoriasis is a chronic, recurrent, inflammatory skin disease that alters the quality of life. Systemic therapy and biologic agents are prescribed for severe and widespread psoriasis, but these drugs may have systemic side effects and immune suppression. Narrowband Ultraviolet B (NB-UVB) phototherapy remains one of the most effective and safe treatments for psoriasis.

Methods: This study was an observational retrospective cohort with one group pretest and post-test design. A retrospective analysis was done on 16 medical records of patients who met the inclusion criteria. The efficacy of the therapy was identified and analyzed using the SPSS version 17 for Windows.

Results: This study found that 16 psoriasis patients received NB-UVB phototherapy, 11 (68.75%) in men and 5 (31.25%) in women. The mean age was 47.31 years. There was a statistically significant difference in the reduction in PASI score before and after receiving combination methotrexate with 24 sessions of NB-UVB phototherapy ($p=0.000$); the delta PASI score was 45,02%. A statistical analysis based on the number of phototherapy sessions per week showed enhanced results when patients attended 3 phototherapy sessions per week ($p = 0.001$).

Conclusion: There was a statistically significant reduction in PASI score in psoriasis vulgaris patients before and after receiving combination methotrexate with 24 sessions of NB-UVB phototherapy.

Keywords: Psoriasis Vulgaris, Phototherapy, Narrowband Ultraviolet B, Methotrexate, Human and Disease.

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INTRODUCTION

Psoriasis is a chronic inflammatory skin disease involving genetic, immune defects, hormones, and environmental factors. Psoriasis vulgaris is often characterized by thick, erythematous, well-demarcated, coarse, layered, silvery-white plaques.¹ Psoriasis vulgaris, also called plaque-type psoriasis, is the most common type, occurring in about 90% of patients.¹

Psoriasis is a chronic, recurrent, inflammatory skin disease that interferes with the quality of life, so appropriate, safe and effective therapy is needed.² The treatment options include topical therapy,

phototherapy, systemic, and biological agents. Systemic treatment and biologic agents are prescribed for severe and widespread psoriasis but cause systemic side effects and immune suppression, which are not tolerable for the patient. It requires alternative or combination therapy.² Narrowband Ultraviolet B (NB-UVB) phototherapy is relatively safe and effective as a treatment modality if used in erythemogenic doses with wavelengths between 311-313 nm, causing good remission in psoriasis lesions.^{1,3}

Based on those mentioned above, this study aims to evaluate the effect of combination methotrexate with 24

sessions of NB-UVB phototherapy in psoriasis vulgaris patients at Dermatology and Venereology Outpatient Department Dr. Soetomo Surabaya from March 2019 to February 2020.

METHODS

This study was an observational retrospective cohort with one group pretest and post-test design that aimed to evaluate the Psoriasis and Severity Index (PASI) score of psoriasis vulgaris patients who received a combination of methotrexate with 24 sessions of NB-UVB phototherapy using secondary data in the form of the medical record.

The inclusions criteria were all patients recorded in medical records with a diagnosis of moderate-severe psoriasis vulgaris who received combination therapy methotrexate with 24 sessions of NB-UVB phototherapy at Dermatology and Venereology Outpatient Department, Dr. Soetomo Surabaya, for the period of March 2019 - February 2020. The exclusions criteria were patients who stopped NB-UVB phototherapy treatment for more than 3 sessions consecutive weeks. The variable in this study was psoriasis vulgaris patients who received combination therapy methotrexate with 24 sessions of NB-UVB phototherapy and assessed based on the Psoriasis and Severity Index (PASI) score. Those data inputted into a data collection sheet to be analyzed using the Statistical Package for Social Sciences (SPSS) version 17 for Windows.

RESULTS

There were 16 psoriasis patients who received NB-UVB phototherapy at Dermatology and Venereology Outpatient Department Dr. Soetomo Surabaya for March 2019-February 2020, which met the inclusion criteria. Patients' demographic data were assessed based on gender, age, Fitzpatrick's skin phototype, and the severity degree based on the PASI scores.

The demographic distribution of psoriasis vulgaris patients received NB-UVB phototherapy (Table 1). The results showed that male patients were more female, 11 (68.75%) males and 5 (31.25%) females. The median age was 47.31 years, with the youngest being 22 years and the oldest was 64 years old. Based on the PASI scores, the severity degree was 5 patients (31.25%) for moderate and 11 patients (68.75%) for severe. Skin types based on Fitzpatrick's phototype were 2 patients (12.55%) with type III, 9 patients (56.25%)

with type IV, and 5 patients (31.25%) with type V (Table 1).

For the initial dose of NB-UVB phototherapy, 16 (100.00%) patients received an initial dose of NB-UVB phototherapy of 260 mJ (Table 1). The methotrexate dosage distribution in psoriasis vulgaris patients who received 24 sessions of NB-UVB phototherapy, as many as 1 (6.25%) patient received 2,5 mg methotrexate therapy, 3 (18.75%) patients received methotrexate 5 mg, 2 (12.5%) patients received 7,5 mg methotrexate, 5 (31.25%) patients received 10 mg

methotrexate, and 5 (31.25%) patients received 15 mg methotrexate (Table 1).

The additional systemic therapy in psoriasis vulgaris patients who received NB-UVB phototherapy, as many as 16 (100.00%) patients received folic acid and 16 (100.00%) patients received cetirizine, respectively, due to the itching (Table 1). The topical therapy in psoriasis vulgaris patients who received NB-UVB phototherapy, as many as 1 (6.25%) patient received clobetasol propionate, 15 (93.75%) patients received desoximetasone, 13 (81.25%) patients

Table 1. Psoriasis vulgaris patient distribution who received a combination of methotrexate with 24 sessions NB-UVB phototherapy

Variable	Total (n=16)
Gender, n (%)	
Male	11 (68.75)
Female	5 (31.25)
Age, Median (Minimum-Maximum)	47.31 (22-64)
Psoriasis and Severity Index (PASI) scores, n (%)	
Moderate (5-10)	5 (31.25)
Severe (>10)	11 (68.75)
Fitzpatrick's Skin Phototypes, n (%)	
I	0 (0.00)
II	0 (0.00)
III	2 (12.50)
IV	9 (56.25)
V	5 (31.25)
VI	0 (0.00)
Narrowband Ultraviolet B (NB-UVB) (260 mJ), n (%)	16 (100.00)
Methotrexate Distribution (mg), n (%)	
2.5	1 (6.25)
5	3 (18.75)
7.5	2 (12.5)
10	5 (31.25)
15	5 (31.25)
Additional Systemic Therapy, n (%)	
Folic Acid	16 (100.00)
Cetirizin	16 (100.00)
Topical Therapy Distribution, n (%)	
Clobetasol propionate	1 (6.25)
Desoximetasone	15 (93.75)
Mometasone furoate	13 (81.25)
Desonide lotion	3 (18.75)
Atopiclair	7 (43.75)
Vaseline album	7 (43.75)
Urea 10%	2 (12.50)
Ketoconazole shampoo	4 (25.00)

Table 2. Evaluation of the PASI scores of psoriasis vulgaris patients before and after receiving 24 sessions of NB-UVB phototherapy

PASI scores before phototherapy (Mean±SD)	PASI scores after 24 sessions of phototherapy (Mean±SD)	Delta PASI scores (Mean±SD)	Delta PASI scores (%)	p
12.65±4.82	7.20±4.82	5.45±3.05	45.02±21.10	0.000*

PASI: Psoriasis and Severity Index; SD: Standard Deviations; *Kruskal-Wallis Test: Statistically significant if p-value less than 0.05

Table 3. The comparison of the significant reduction of PASI scores in psoriasis vulgaris patients after receiving a combination of methotrexate with NB-UVB phototherapy

Variable	n	PASI scores before phototherapy	PASI scores after 24 sessions of phototherapy	Delta PASI scores	p
Gender					
Male	11	13.28	9.20	4.00	0.080
Female	5	13.20	6.51	6.69	
Age (Years Old)					
< 60	13	13.41	7.65	5.76	0.304
≥ 60	3	12.75	6.17	6.50	
Methotrexate (mg)					
≤ 5	4	10.80	6.30	4.25	0.323
> 5-10	7	13.78	7.97	5.81	
> 10	5	15.00	7.40	7.60	
Topical					
Steroid, emollient	12	13.87	8.03	5.79	0.458
Steroid, emollient, antifungal shampoo	4	11.25	4.92	6.33	
Phototherapy session (per week)					
3 sessions	7	13.00	4.65	8.27	0.001*
< 3 sessions	9	13.48	9.66	3.82	

PASI: Psoriasis and Severity Index; *Kruskal-Walis Test: Statistically significant if p-value less than 0.05

received mometasone furoate, 3 (18.75%) patients received desonide lotion, 7 (43.75%) patients received atopiclair, 7 (43.75%) patients received vaseline album, 2 (12.50%) patients received urea 10%, and 4 (25.00%) scalp psoriasis patients received ketoconazole shampoo (Table 1).

The evaluation of the PASI scores in psoriasis vulgaris patients before and after receiving 24 sessions of NB-UVB phototherapy with the mean PASI scores before receiving NB-UVB phototherapy was 12.65 ± 4.82 . The mean PASI scores after receiving 24 sessions of NB-UVB phototherapy was 7.20 ± 4.82 . The mean delta PASI scores or the mean reduction of PASI scores before and after receiving 24 sessions of NB-UVB phototherapy was 5.45 ± 3.05 . The mean delta of the PASI scores (%) or the mean reduction of PASI scores (%) before and after receiving 24 sessions of NB-UVB phototherapy was 45.02 ± 21.10 . From the statistical analysis, the p-value was 0.000, indicating a statistically significant difference in reducing PASI scores before and after receiving 24 sessions of NB-UVB phototherapy (Table 2).

The comparison of the significance values for reducing PASI scores by gender, age, methotrexate dosage, combination topical therapy, and the number of phototherapy sessions per week in psoriasis

vulgaris patients receiving a combination of methotrexate with 24 sessions of NB-UVB phototherapy (Table 3). The mean delta of PASI scores in males was 4,00 and in females was 6,69 ($p = 0,080$), which indicated that there was no statistically significant difference between male and female ($p > 0.05$) towards the reduction of PASI scores in psoriasis vulgaris patients after receiving 24 sessions of NB-UVB phototherapy (Table 3).

The mean delta of PASI scores at < 60 years of age of 5.76 and at ≥ 60 years of 6.50 ($p = 0.304$) which indicated that there was no statistically significant difference between ages < 60 years and ≥ 60 years of age for the reduction of PASI scores in psoriasis vulgaris patients after receiving a combination of methotrexate with 24 sessions of NB-UVB phototherapy (Table 3).

The reduction in the PASI scores is based on the methotrexate dosage using the Kruskal-Wallis test. Kruskal-Wallis test was a different test for 3 groups for abnormal distribution obtained the mean delta PASI scores at the methotrexate dose ≤ 5 mg was 4.25, > 5 mg - 10 mg was 5.81, > 10 mg was 7.60 ($p = 0.323$), which indicated that there was no statistically significant difference based on the differences of the methotrexate dosage in the reduction in PASI scores in psoriasis vulgaris patients

after receiving 24 sessions of NB-UVB phototherapy (Table 3).

The PASI scores reduction based on topical combination therapy showed that the mean delta PASI scores for the combination of topical steroids and emollients was 5.79 and for the combination of topical steroids, emollients, and anti-fungal shampoos was 6.33 ($p = 0.458$), which indicates that there was no statistically significant difference between the combination of topical corticosteroid and emollient therapy with the combination of topical corticosteroid therapy, emollient and anti-fungal shampoo on the reduction of PASI scores in psoriasis vulgaris patients after receiving the combination of methotrexate with 24 sessions of NB-UVB phototherapy (Table 3).

The reduction in PASI scores based on the number of phototherapy sessions per week showed that the mean delta PASI scores on phototherapy with 3 sessions per week was 8.27 and < 3 sessions per week was 3.82 ($p = 0.001$), which showed that there was a statistically significant difference between the 3 sessions per week and < 3 sessions per week of phototherapy on the reduction of PASI scores in psoriasis vulgaris patients after receiving a combination of methotrexate with 24 sessions of NB-UVB phototherapy (Table 3).

DISCUSSION

This retrospective study found that 16 psoriasis vulgaris patients received a combination of methotrexate with 24 sessions of NB-UVB phototherapy at Dermatology and Venereology Outpatient Department Dr. Soetomo Surabaya from March 2019 to February 2020. The gender distribution of psoriasis vulgaris showed that males were more than females, 11 (68,75%) males and 5 (31,25%) females. The clinical manifestations of psoriasis in males were often more severe, so males often came to the hospital for treatment.^{1,3} Male also tend to have a higher BMI than women, and the influence of smoking and alcohol consumption, likely to be higher in males, is a risk factor for psoriasis.^{4,5} A study in Korea found that the prevalence of psoriasis increased around 50 years old.⁶ This was due to the increasing comorbid risk factors in old age, namely obesity, metabolic disease, stress, and susceptibility to infections which could be a risk factor for psoriasis.⁷

A nonrandomized control trial on moderate-severe patients given NB-UVB phototherapy was shown to reduce the PASI scores. In general, NB-UVB phototherapy is recommended for moderate-severe psoriasis vulgaris.⁸ NB-UVB was the first-line phototherapy for moderate-severe plaque-type psoriasis vulgaris with an extensive skin involvement accompanied by thick plaques. In moderate-severe psoriasis vulgaris, there was an increase in the intensity of redness, desquamation, and extensive plaque thickness. NB-UVB phototherapy could improve redness, desquamation, and extensive plaque thickness by inducing apoptosis of keratinocytes and T cells in the epidermis and dermis, increasing immunosuppression by promoting migration of Langerhans cells from the epidermis and reducing degranulation of mast cells and release of histamine, and inducing changes in the cytokine of psoriasis.⁹

The characteristics of Asian skin based on Fitzpatrick's skin phototype obtained types III and IV in Chinese and Japanese and types IV and V in South Asian, Indian and Pakistani populations (10). The distribution of the initial dose of NB-UVB phototherapy was 16 (100%)

patients received an initial dose of 260 mJ. Erythema skin reactions due to burning during and after Narrowband ultraviolet B (NB-UVB) phototherapy may occur, which caused a dose adjustment.^{1,8} Determination of the initial dose of NB-UVB phototherapy with 260 mJ in all psoriasis vulgaris patients who received narrowband ultraviolet B (NB-UVB) phototherapy may be considered to avoid the risk of unwanted side effects such as erythema due to burning during and after receiving NB-UVB phototherapy and the initial dose of NB-UVB phototherapy with 260 mJ was already efficient in achieving improvement.

In moderate-severe psoriasis, methotrexate could be combined with NB-UVB phototherapy.¹⁰ Methotrexate is a folic acid analog that competitively inhibits dihydrofolate reductase and other folate-related enzymes. The main effect of methotrexate is to inhibit the synthesis of thymine and purines, which results in a reduction of DNA and RNA synthesis, inhibits mitosis and cell proliferation, including psoriatic keratinocytes. Inhibition of nucleic acid formation in activated T cells and keratinocytes is the main mechanism of action of methotrexate as an antiproliferative and immunomodulation in psoriasis vulgaris.¹¹

A recent meta-analysis of randomized controlled trials showed a 79% reduction in mucosal and gastrointestinal side effects when folic acid supplementation was given to the patients who received systemic methotrexate therapy for psoriasis vulgaris. Various studies have been conducted to prevent the side effects of methotrexate by using folic acid supplementation while maintaining the therapeutic benefits of methotrexate.¹² The treatment for pruritus in psoriasis vulgaris is still debated because its pathogenesis is still not fully understood. Pruritus is more common in psoriasis vulgaris than in other types of psoriasis. It can interfere with the patients' quality of life. Many investigators had suggested impaired innervation and dysregulation of neuropeptide expression in psoriasis. As an important mediator in allergic, especially urticaria, histamine is not a causative agent in psoriasis.¹³

A study conducted topical administration of high potency

corticosteroids could improve in 75% of patients with moderate-severe psoriasis vulgaris. The mechanism of action of topical corticosteroids is anti-inflammatory, antiproliferative, immunosuppressive, and vasoconstrictive. Topical corticosteroids in moderate-severe scalp psoriasis have also been effective in reducing plaque thickness. Combination with topical therapies such as corticosteroids and emollients while undergoing Narrowband Ultraviolet B (NB-UVB) phototherapy had been proven safe, effective and had the potential to increase efficacy.¹⁴

Anti-fungal ketoconazole was shown to be effective in reducing the colonization of *Pityrosporum* sp. in scalp psoriasis.¹⁵ It interacted with microbial products by causing an abnormal skin response in psoriasis. Microbial products that had a role in the pathogenesis of psoriasis were *Malassezia ovalis* (*Pityrosporum ovale*), a normal flora in the scalp, which could enhance the activation of the pathogenesis pathway, which could lead to psoriasis lesions. *Malassezia ovalis* is also believed to increase the development of scalp psoriasis.¹⁶

There was no difference between gender and age in the clearance rate of psoriasis vulgaris lesions after receiving Narrowband Ultraviolet B (NB-UVB) phototherapy. IL-17 and IL-23 levels after receiving NB-UVB phototherapy in both males and females, as well as ages, decreased significantly.¹⁷ IL-17 and IL-23 levels are known to be associated with the pathogenesis of psoriasis as a predictive factor for the prognosis and the successful response of NB-UVB phototherapy.¹⁸ There was no difference between gender and age in reducing the PASI scores after receiving NB-UVB phototherapy. The significant difference in lowering PASI scores was the NB-UVB phototherapy.¹⁹

A study recommends the dose of methotrexate between 5-15 mg per week, 60% of patients achieved a reduction in PASI scores by 75% for the initial dose of methotrexate 15 mg per week for 16 weeks, for a dose of 7,5 mg per week, a reduction in PASI scores was 40%.²⁰ A study on 39 patients who received a combination of narrowband ultraviolet B (NB-UVB) phototherapy with methotrexate 0.4 mg/kg/week and maximum dosage of 25

mg/week showed that this combination therapy gave a rapid clinical improvement and there was a significant reduction in PASI scores in all psoriasis vulgaris patients.²¹

Although the dose of methotrexate at the onset of NB-UVB phototherapy varies, the combination of methotrexate and NB-UVB phototherapy will work synergistically. Methotrexate and NB-UVB phototherapy both have antimitotic and antiproliferative functions against T lymphocytes, and both have an anti-inflammatory property. Methotrexate can help reduce the squama and infiltration of psoriasis lesions, thus allowing NB-UVB phototherapy to penetrate deeper into the dermis. It has greater effectiveness in reducing dermal T lymphocytes.²²

A study in Taiwan showed that 98,4% of psoriasis vulgaris patients received topical therapy with corticosteroids and emollients, there was a significant improvement in psoriasis vulgaris plaque lesions.²³ Other topical treatments combined with topical anti-fungal therapy were safe and effective, especially in scalp psoriasis. In psoriasis, there is an involvement of *Malassezia ovalis* (*Pityrosporum ovale*), a normal flora in the scalp. Still, in some psoriasis patients, even though *Malassezia ovalis* (*Pityrosporum ovale*) is a normal flora, it can enhance the activation of cytokines, chemokines, and PGE2. It is associated with Th1 and Th2 from mononuclear cells, leading to new scalp lesions.¹⁶

The three sessions per week of NB-UVB phototherapy caused a high cumulative dose, which increased inflammatory factor expression changes through the NF- κ B signaling pathway.²⁴ NB-UVB phototherapy with a high cumulative dose could also increase inhibition of pro-inflammatory factor expression and increase anti-inflammatory factor expression through increased induction of lymphocyte apoptosis, reduced pro-inflammatory cytokine production, down-regulation of the Th17 signaling pathway, and reduction of T cell depletion, so it could be faster in reducing or thinning plaque in psoriasis lesions which was an important mechanism for psoriasis therapy.²⁵ The limitation of this study is the relatively small group of patients and the data was based on medical records, which

caused a numerous risk of bias. Further study is needed to evaluate the PASI scores over 24 sessions of NB-UVB phototherapy to know the number of sessions that effectively reduce the PASI-75 scores in psoriasis vulgaris patients.

CONCLUSION

The conclusion is there was a statistically significant difference in the reduction in PASI scores before and after receiving a combination of methotrexate with 24 sessions of NB-UVB phototherapy. Combining methotrexate with 24 sessions of NB-UVB phototherapy may be considered for patients with moderate-severe psoriasis vulgaris who failed with previous therapy. The importance of routine control is for the compliance to receive 3 sessions of narrowband ultraviolet B (NB-UVB) phototherapy per week in order to achieve a reduction in the PASI-75.

CONFLICT OF INTEREST

There is no conflict of interest regarding the manuscript

ETHICS CONSIDERATION

This research has obtained ethical approval from the Ethics Committee of Dr. Soetomo General Academic Teaching Hospital Surabaya (0142/LOE/301.4.2/X/2020).

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AUTHOR CONTRIBUTIONS

All authors equally contribute to the study from the conceptual framework, data acquisition, data analysis until reporting the results of the study through publication.

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