Cutaneous Reactions Complicated from Phototherapy in Thai Patients with Dermatological Diseases: A Retrospective Study

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Abstract

The phototoxic reaction is one of phototherapy's most significant adverse effects. This retrospective, single-center study in the dermatology department aims to describe the prevalence of phototoxic reactions related to Phototherapy in Thai patients. All phototherapy patients had 64,629 sessions between October 2015 and September 2020. The 200 sessions (0.3%) of phototoxic responses were associated with phototherapy. The dermatosis with the most significant incidence of phototoxic reactions was vitiligo (54%). The most common cause of phototoxicity was the treatment protocol (49.5%), followed by other causes (26%), a patient variable as compliance, e.g., excessive exposure to sunlight (9%), medication (8.5%), loss of treatment (6%), displacement of underwear from the previous visit (2.5%), and concurrent disease (2%). Dermatologist needs to be aware of when to continue to pursue step up the dose and also emphasize to the patient to comply with compliance to the treatment.

Keywords*: *Phototoxic reaction, Adverse events, Phototherapy, Narrowband UVB, Excimer lamp, Psoralen plus UVA

1. Introduction

Phototherapy uses ultraviolet (UV) radiation to treat dermatological conditions, such as psoriasis, vitiligo, atopic dermatitis, photodermatoses, pityriasis lichenoides, lymphomatoid papulosis, seborrheic dermatitis, pruritus, cutaneous lymphomas. Currently, phototherapy encompasses irradiation with broadband UVB (290-230 nm), narrowband UVB (311-313 nm), 308 nm excimer laser, UVA1 (340-400 nm), UVA (320-400 nm) plus psoralens (PUVA) or alone (Honigsmann, & Schwarz, 2018; Singer, & Berneburg, 2018).

Phototherapy can cause adverse events (AEs) as phototoxic or photoallergic reactions. A phototoxic response is obtained when topical and systemic drugs or their metabolites absorb light inducing direct cellular damage. It can occur in all individuals exposed to adequate doses of the agent and the activating wavelengths of radiation. A photoallergic reaction is a type IV delayed hypersensitivity response to a molecule modified by the absorption of photons. Characteristic features of phototoxic reactions mainly as an exaggerated sunburn but also as prickling, burning, blistering, pseudoporphyria, photo-onycholysis, hyperpigmentation, hypopigmentation (vitiligo-like lesions), telangiectasia, purpura, pellagra-like reactions, actinic keratosis and skin cancer and accelerated photoaging. The phototoxic reaction can be caused by UV overdose, failure by patients to take appropriate photoprotective measures, Fitzpatrick skin type, sun-expose time, light skin phototype, phototoxic agents, drugs, and environment (Pereira et al., 2022; Henry, 2019; Ibbotson, 2018).

In Psoriasis phototherapy, several studies have corroborated the greater efficacy of PUVA compared with NB-UVB in plaque-type psoriasis (Singer, & Berneburg, 2018; Elmets et al., 2020; Armstrong, & Read, 2020; Almutawa et al., 2013; Chen et al., 2013). Based on clearance outcome, some studies show that PUVA is more effective than NB-UVB, followed by BB-UVB and bath PUVA (Almutawa et al., 2013). Although oral PUVA has superior efficacy to UV-B in treating psoriasis, it is no longer preferred due to the development of skin cancer with long-term use. Moreover, NBUVB did not harm pregnant women and Asian children (Singer, & Berneburg, 2018; Elmets et al., 2020; Armstrong, & Read, 2020; Chen et al., 2013; Van et al.,

2019; Stern, 2012; Kemény, Varga, & Novak, 2019). For mild psoriasis, a 308-nm Excimer laser is most helpful in treating limited areas (Kemény, Varga, & Novak, 2019; Matos, Ling, & Sheth, 2016).

For Vitiligo phototherapy, most studies have demonstrated that NB-UVB has superior efficacy compared with other forms of phototherapy; NB-UVB is now considered the first-line treatment modality for generalized vitiligo. Besides its effectiveness, NB-UVB has a better safety profile than PUVA, mainly due to the absence of adverse effects related to psoralen (Thu et al., 2019; Bae et al., 2017; Esmat et al., 2017). Hong, Park, and Lee (2005) found that excimer laser had greater efficacy than NB-UVB in treating vitiligo. In addition, several recent meta-analyses have shown similar efficacy between excimer light, excimer laser, and NB-UVB for treating vitiligo (Esmat et al., 2017).

Phototherapy in atopic dermatitis is a second-line treatment after the failure of first-line therapy (emollients, topical corticosteroids, and topical calcineurin inhibitors) **(**Rodenbeck, Silverberg, & Silverberg, 2016). Several studies have found that NB-UVB produces better improvement in AD severity scores than UVA-1, while other studies have not found statistically significant differences between UVA-1 and NB-UVB therapies. Excimer laser (308 nm) may be a good option for localized refractory AD lesions. The safe use of NBUVB in children has been well documented (Ortiz-Salvador, & Pérez-Ferriols, 2017).

There have been numerous adverse effects (AEs) of phototherapy in clinical practice. The lack of a definitive treatment leads to suffering rather than a cure, despite Phototherapy being a conventional therapeutic method and under control. In Institute of Dermatology, Thailand, still has an increasing rate of phototoxicity of 40 persons/per year. An improved understanding of the prevalence and risk factors of phototoxic reactions related to phototherapy may help physicians to advise patients better during treatment, potentially allowing for the prevention of phototoxicity. However, no audits concerning the prevalence and risk factors of phototoxic reactions related to phototherapy have been published, particularly in regions with extended sun exposure, such as Thailand. To better access to the safety of phototherapy, this study aimed to describe the prevalence and risk factors of phototoxic reactions in patients treated with phototherapy in Thai patients at the Institute of Dermatology, Thailand.

2. Objectives

To describe the prevalence of cutaneous reactions related to Phototherapy in Thai patients at the Institute of Dermatology, Thailand.

3. Materials and Methods

All patients who visited the Radiobiology Department, the Institute of Dermatology, Thailand, between October 2015 and September 2020 were the subjects of this single-center, retrospective study. The phototherapy-induced phototoxic reaction is the diagnosis. A dermatologist evaluated the diagnosis. A level of phototoxicity was divided into grades 0-4. Treatments included in the study were: NB-UVB, systemic PUVA, topical PUVA, ultraviolet A (UVA), and 308 nm excimer lamp. In all systemic and topical PUVA, 8-methoxypsoralen (8-MOP) was used. In systemic PUVA, pre-phototherapy examinations included an eye exam by an ophthalmologist and a blood test with an antinuclear antibodies (ANA) test, which was also evaluated in other treatment modalities if there was a clinical suspicion of lupus. According to the patient's Fitzpatrick skin type, the initial UV doses were selected after the suggested fixed dosages.

The following information was collected retrospectively: dermatological disease to treat, sex, age, Fitzpatrick skin type, underlying disease, current medications during phototherapy, phototherapy modality, start dose/ increment dose, current cycle, phototoxic dose, total cumulative dose, level of phototoxicity (grade 0-4), causes of phototoxicity. The levels of phototoxic reactions considered were: grade 0 (defined as severe generalized itching, burning sensation, no erythema), grade 1 (defined as minimal perceptible erythema), grade 2 (defined as well-defined asymptomatic erythema), grade 3 (defined as symptomatic erythema persisting more than 24 hr), grade 4 (defined as severe erythema with edema, blister). The causes of phototoxic reactions were: Treatment protocol (dose UVA/UVB too high), Patient variable (Medication ex. MTX, Doxycycline, Diuretic, Coal tar), Concurrent disease, Loss treatment, Excessive exposure to sunlight, and Others.

Demographic and descriptive data were expressed as absolute and relative frequencies for categorical variables and as medians and interquartile range (IQR) for non-normally distributed quantitative variables. The χ^2 test was used to compare AE incidence between sex, occupation, season, or skin types; the Mann-Whitney U test to compare non-normally distributed quantitative variables; the Binary Logistic Regression to predict the relationship between multiple factors (dichotomous); the Multiple Logistic Regression to predict the relationship between a factor and doses. The magnitude of associations was measured using an odds ratio (OR) with 95% confidence intervals (95% CI). P-values <0.05 were considered statistically significant. All analyses were performed using Excel and IBM SPSS Statistics for Macintosh, Version 23, Licence No. 1975-01566-C.

4. Results and Discussion

4.1 Results

Between October 2015 and September 2020, 64,629 phototherapy treatments were administered to patients at the Institute of Dermatology, Thailand. This study recruited 200 participants (30.5% male and 69.5% female, with a median age of 45.21). The onset of developing cutaneous reaction following the last treatment session was after receiving phototherapy. They met both inclusion and exclusion criteria before starting the research protocol. There were 12 (6%) aged under 20 years. The most common type was Fitzpatrick skin type IV as displayed by 81.5% (n=163) of individuals, was, followed by type III (12.5%; n=25) and type V in (6%; n=12). This study contained no participants with Fitzpatrick skin types I, II, or VI.

During the study, 200 (0.3%) phototoxic reactions were recorded. The main dermatosis treated was vitiligo (54%), followed by Psoriasis vulgaris (24%), Mycosis fungoides (13.5%), Pityriasis alba (3%), Pityriasis lichenoides chronica (1.5%), Atopic dermatitis, Prurigo nodularis, Pityriasis lichenoides, et varioliformis acuta, Actinic Prurigo, Granuloma annulare, and Localized scleroderma, all of which had a 0.5% prevalence. Clinical and epidemiological characteristics according to phototoxicity are shown in Table 1.

Table 1 Clinical and epidemiological characteristics according to phototoxicity

	Total (n=200)
Sex, *n (%)*	
Male	61 (30.5)
Female	139 (69.5)
Age	
Years, mean ± (SD)	45.21 (16.01)
Skin Type, *n (%)*	
I and II	0 (0)
III	25 (12.5)
IV	163 (81.5)
V	12 (6.0)
VI	0 (0)
Dermatosis, *n (%)*	
Vitiligo	108 (54.0)
Psoriasis vulgaris	48 (24.0)
Mycosis fungoides	27 (13.5)
Pityriasis alba	6 (3.0)
Pityriasis lichenoides chronica	3 (1.5)
Atopic dermatitis	1 (0.5)
Prurigo nodularis	1 (0.5)
Pityriasis lichenoides	1 (0.5)
Actinic Prurigo	1 (0.5)
Granuloma annulare	1 (0.5)
Localized scleroderma	1 (0.5)
Other[a]	2 (1.0)

[a]Other skin changes due to chronic exposure to nonionizing radiation. SD: standard deviation.

The primary cause of phototoxicity was the treatment protocol (UVA/UVB dose too high) (49.5%; n=99) of the treatments, followed by other causes (e.g., thin skin, rubbing the lesion, wearing various protection, etc.) (26%; n=52), excessive exposure to sunlight (9%; n=18), medication (e.g., Methotrexate, Doxycycline, Diuretic, Coal tar) (8.5%; n=17), loss of treatment (6%; n=12), displacement of underwear from the previous visit (2.5%; n=5), technical error (Incorrect dose/ addition of UVB Instead of UVA radiation) (2.5%; n=5) and concurrent disease (2%; n=4). The causes of phototoxicity according to Phototherapy are shown in Table 2.

Table 2 The causes of phototoxicity according to Phototherapy

Cause of Phototoxicity	Total *n (%)*
Treatment protocol[a]	99 (49.5)
Patient variable: Medication[b]	17 (8.5)
Patient variable: Concurrent diseases	4 (2.0)
Patient variable: Loss Treatment	12 (6.0)
Patient variable: Excessive exposure to sunlight	18 (9.0)
Patient variable: Displacement of underwear from the previous visit	5 (2.5)
Technical error[c]	5 (2.5)
Other causes	52 (26.0)

[a]Treatment protocol: Dose UVA/UVB too high; [b]Patient variable: Medication ex. Methotrexate, Doxycycline, Diuretic, Coal tar; [c]Technical Error - Incorrect dose/ addition of UVB Instead of UVA radiation. [d]Other causes: thin skin, rubbing the lesion, wearing various protection sizes, etc.

In all 200 patients, phototoxicity grade 3 was mostly found in females 55% (n=110) and males 19.5% (n=39). All phototoxicity grades are between the age range of 40 to 50-year-olds. Patients with Fitzpatrick skin type IV (81.5%; n=163) had the highest incidence of phototoxic response in grade 3 (61.5%; n=123), followed by grade 4 (10%; n=20), grade 2 (7%; n=14), and grade 1 (3%; n=6). There were 12.5% (n=25) patients with Fitzpatrick skin type III and 6% (n=12) with type VI. In 41.5% (n=83) of Vitiligo patients, a grade-3 phototoxic response was observed, followed by grade 4 (10.5%; n=21). In 17% (n=34) of patients with Psoriasis vulgaris, grade 3 phototoxicity was observed, followed by grade 2 (4%; n=8). In 10.5% (n=21) of patients, Mycosis fungoides, grade 3 phototoxicity was observed, followed by grade 2 (3%; n=6).

The diagnosis (p=0.002), concurrent disease (p=0.002), and excessive exposure to sunlight (p=0.029) were statistically significant compared to the level of phototoxicity. Participants' characteristics according to the level of phototoxicity are shown in **Table 3.**

Table 3 Clinical and epidemiological characteristics according to the level of phototoxicity

Variables	Level of phototoxicity				p-value
	Grade 1 *(n=6)*	Grade 2 *(n=21)*	Grade 3 *(n=149)*	Grade 4 *(n=24)*	
Sex, *n (%)*					NS
Male	2 (33.3)	9 (42.9)	39 (26.2)	11 (45.8)	
Female	4 (66.7)	12 (57.1)	110 (73.8)	13 (54.2)	
Age					NS
Years, mean ± (SD)	48.83 (11.55)	43.52 (14.01)	45.4 (16.34)	44.54 (17.12)	
Skin Type, *n (%)*					NS
I and II	0 (0)	0 (0)	0 (0)	0 (0)	N/A
III	0 (0)	5 (23.8)	18 (12.1)	2 (8.3)	NS
IV	6 (100.0)	14 (66.7)	123 (82.6)	20 (83.3)	NS
V	0 (0)	2 (9.5)	8 (5.4)	2 (8.3)	NS
VI	0 (0)	0 (0)	0 (0)	0 (0)	N/A

Variables	Level of phototoxicity				p-value
	Grade 1 *(n=6)*	Grade 2 *(n=21)*	Grade 3 *(n=149)*	Grade 4 *(n=24)*	
Dermatosis, *n (%)*					0.002
Vitiligo	1 (16.7)	3 (14.3)	83 (55.7)	21 (87.5)	
Psoriasis vulgaris	3 (50.0)	8 (38.1)	34 (22.8)	3 (12.5)	
Mycosis fungoides	0 (0)	6 (28.6)	21 (14.1)	0 (0)	
Pityriasis alba	2 (33.3)	2 (9.5)	2 (1.3)	0 (0)	
PLC	0 (0)	1 (4.8)	2 (1.3)	0 (0)	
Atopic dermatitis	0 (0)	0 (0)	1 (0.7)	0 (0)	
Prurigo nodularis	0 (0)	0 (0)	1 (0.7)	0 (0)	
PLEVA	0 (0)	0 (0)	1 (0.7)	0 (0)	
Pityriasis lichenoides chronica	0 (0)	0 (0)	1 (0.7)	0 (0)	
Actinic Prurigo	0 (0)	0 (0)	1 (0.7)	0 (0)	
Granuloma annulare	0 (0)	0 (0)	1 (0.7)	0 (0)	
Localized scleroderma	0 (0)	1 (4.8)	0 (0)	0 (0)	
Other[a]	0 (0)	0 (0)	2 (1.3)	0 (0)	
Cause of Phototoxicity, *n (%)*					
Treatment protocol[b]	4 (66.7)	8 (38.1)	80 (53.7)	7 (29.2)	NS
Patient variable: Medication[c]	0 (0.0)	0 (0.0)	15 (10.1)	2 (8.3)	NS
Patient variable: Concurrent disease	1 (16.7)	2 (9.5)	1 (0.7)	0 (0.0)	0.002
Patient variable: Loss Treatment	0 (0.0)	3 (14.3)	8 (5.4)	1 (4.2)	NS
Patient variable: Excessive exposure to sunlight	0 (0.0)	1 (4.8)	11 (7.4)	6 (25.0)	0.029
Patient variable: Displacement of underwear from the previous visit	0 (0.0)	1 (4.8)	4 (2.7)	0 (0.0)	NS
Technical error[d]	0 (0.0)	1 (4.8)	2 (1.3)	2 (8.3)	NS
Other causes[e]	1 (16.7)	6 (28.6)	36 (24.2)	9 (37.5)	NS

[a]Other skin changes due to chronic exposure to nonionizing radiation. PLC: Pityriasis lichenoides chronica.; PLEVA: Pityriasis lichenoides et varioliformis acuta.; [b]Treatment protocol: Dose UVA/UVB too high; [c]Patient variable: Medication ex. Methotrexate, Doxycycline, Diuretic, Coal tar; [d]Technical Error - Incorrect dose/ addition of UVB Instead of UVA radiation; [e]Other causes: thin skin, rubbing the lesion, wearing various protection sizes, etc.; SD: standard deviation; NS: not significant.

4.2 Discussion

Many variables, including equipment, staff, and working methods, can affect the frequency and severity of phototherapy-related adverse effects. No specific guidelines on managing adverse events with phototherapy exist. There are no reports about the prevalence of phototoxic reactions related to phototherapy, particularly in regions with extended sun exposure, such as Thailand. This study is the first to establish the prevalence of phototoxic reactions related to phototherapy concerning the total number of treatment sessions in a phototherapy unit.

The incidence of adverse events associated with phototherapy in clinical settings has been extensively reported to range from 0.8% to 94%. Martin et al. (2007) reported that the total number of acute adverse events recorded for all phototherapy treatments was 0.8% (70 of 8784 treatments). The report by Belinchon et al. (2020) noted the rate of AEs with Phototherapy was 19.1%. Vazquez et al. (2018) reported that Phototoxic reactions are more frequent in patients with light skin phototypes (I and II). Previously published AE rates for NB-UVB ranged from 10% to 94% (Ibbotson et al., 2004; Green et al., 1988; Coven et al., 1997; Gordon et al., 1999; Green et al., 1992). Phototoxicity due to PUVA in 10.9% of patients. Problems with the treatment protocol were the primary cause (Morison, Marwaha, and Beck, 1997).

According to the findings, NB-UVB phototherapy accounted for 84% of treatments, which aligns with current therapeutic recommendations and several regional, national, and worldwide publications. Vitiligo is the most common dermatosis treated by our phototherapy unit. Phototherapy is a mainstay in vitiligo treatment, with extensive evidence-based and valuable experience for this dermatosis (Ibbotson et al., 2004; Bae et al., 2017). The results showed that the rate of acute adverse events found for more than five years in a working phototherapy unit was low (200 out of 64,629 treatments, 0.3%), and 24 were considered to have grade 4 phototoxic reactions (0.04% of all treatments). There was no difference in the proportion of men and women who experienced adverse effects and no significant differences across skin phototypes. Patients with adverse events were slightly old.

The rate of acute adverse events in this study was low, 0.3%, although around half of these were caused by the treatment protocol (UVA/UVB dose too high). Hence, when presctibed a higher dose, the patient should be informed of the possibility of a phototoxic reaction; once the phototoxic reaction improves, there is no need to increase the dose.

The elderly age was associated with an increasing likelihood of phototoxic reactions and a high level of phototoxicity. Current medications (such as methotrexate, doxycycline, diuretics, and coal tar), exposure to sunlight following treatment, and patients with thin skin are causes of phototoxicity compared to the phototherapy modality. The summertime and concurrent disease (Allergic rhinitis, Supraventricular tachycardia, Thalassemia, Chronic HBV, Fatty liver) were statistically significant concerning the level of phototoxicity. Hence, providing additional information to patients with these risk factors for AEs and enhancing monitoring and control in these groups could assist in the prevention and rapid treatment of AEs, thereby facilitating the completion of the treatment regimen. However, the data included in this study were collected through a clinical audit rather than through traditional research. Therefore, they might be limited by the pressures and errors that could occur in clinical setting practice. In addition, a percentage of patients receiving therapy during this period previously experienced well-tolerated treatment sessions, which might have contributed to the low incidence of adverse events.

Also, it is noted that the adverse event data presented in this study are particular to dose schedules based on pretreatment MED (minimal erythema dose) or MPD (minimal phototoxic dose) testing for each patient. Nevertheless, not all phototherapy units in Thailand follow this regimen. Consequently, the incidence of acute adverse effects, particularly erythema, may vary. Mainly, specific dosage regimens rely on the induction of an erythemal response to calculate dosage increments during the initial phases. This audit's low rate of adverse events demonstrates the advantages of following this regimen.

This study does have some limitations. First, the study is a single-center retrospective investigation carried out in areas with prolonged sun exposure, which may limit the generalization of the results. Secondly, the rareness of some dermatoses might determine findings on dermatoses-related adverse events. Thirdly, the absence of some skin phototypes might prevent judgments regarding dermatosis-related adverse effects. Fourthly, several patients discontinued therapy for unspecified reasons, which might indicate an underestimating of the incidence of adverse events (AEs).

5. Conclusion

This study reports the prevalence of phototoxic reactions related to phototherapy in Thai patients at the Institute of Dermatology, Thailand. The result was low, displayed by 0.3% of phototoxic reactions associated with phototherapy. Vitiligo was the most frequent phototoxic reaction observed. The most common cause of phototoxicity was the treatment protocol (Dose UVA/UVB too high). Many factors including age, concurrent disease, current medications, excessive exposure to sunlight, and thin skin, can influence phototoxic reactions. All of these were associated risk factors for phototoxic reactions during phototherapy. To rapidly detect and manage adverse events (AEs) in patients with these risk factors, physicians should inform them of the possibility of a phototoxic reaction, consider increasing the dosage with caution, and enhance monitoring.

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