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CLINICAL REPORT

No Evidence for Increased Skin Cancer Risk in Koreans with Skin Phototypes III-V Treated with Narrowband UVB Phototherapy

Seong Jin JO, Hyuck Hoon KWON, Mi Ra CHOI and Jai Il YOUN
Department of Dermatology, Seoul National University College of Medicine, Seoul, Korea

Narrowband ultraviolet B (nbUVB) phototherapy is used around the world for the treatment of various skin diseases. However, the carcinogenic risk associated with nbUVB treatment in patients with skin phototypes III–V has not been studied. This retrospective study compared the incidence of skin cancer in Korean patients with skin phototypes III-V treated with nbUVB with that in a control Korean population. A total of 445 nbUVB-treated patients were followed for 1,274 person-years (mean follow-up period 34.4 months). No melanoma cases were detected during the follow-up period. However, one patient developed basal cell carcinoma four months after the start of nbUVB phototherapy. For non-melanoma skin cancer, the expected number of cases was 0.059 and the standardized incidence ratio 17.0 (95% confidence interval 0.4–94.8). There were no statistically significant differences between the nbUVB and control groups. Thus, nbUVB phototherapy using TL-01 lamps seems to be a safe therapeutic modality for patients with skin phototypes III–V. ***Key words: phototherapy; narrowband UVB; Asian; Korean; skin neoplasms*****.**

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Jai Il Youn, MD, PhD, Department of Dermatology, Seoul National University College of Medicine, 28-Yongon-dong, Chongno-gu, Seoul 118-744, Korea. E-mail: jaiil@snu.ac.kr

Since the introduction in the 1980s of the TL-01 lamp (Philips Co., Eindhoven, Netherlands), which emits 313 ± 2 nm ultraviolet B (UVB) light, narrowband UVB (nbUVB) phototherapy has been widely used in the treatment of various diseases, including atopic dermatitis, polymorphic light eruption, vitiligo, and other dermatoses. nbUVB is regarded as a standard form of phototherapy, especially for the treatment of psoriasis, because it is more effective than broadband UVB (bbUVB) and safer than psoralen-ultraviolet A (PUVA) photochemotherapy (1–3).

Since UV rays play an important role in the development of skin cancer (4), clinicians have been concerned about the possible carcinogenic effects of UV-based phototherapy. While a dose-dependent increase in skin cancer risk has been reported in patients treated with PUVA photochemotherapy (5–8), long-term exposure to UVB was not found to be associated with increased risk of squamous cell carcinoma (SCC) (9). Accordingly, nbUVB phototherapy was thought to be reasonably safe in terms of its potential to produce malignancies. However, it has been reported that skin tumors developed more often and earlier in mice treated with nbUVB than in others treated with bbUVB (10–12). Although results from animal studies should not be directly extrapolated to humans, those studies did cast doubt on the safety of nbUVB phototherapy, and human-based studies were subsequently undertaken.

In humans, no definite associations between nbUVB phototherapy and skin cancer were found in retrospective studies carried out in Germany (13), Northern Ireland (14) and Scotland (15). However, these European studies focused on Caucasian patients and their findings may not be applicable to non-Caucasians. It is known that racial differences, including skin color, contribute to differences in reactions to UV exposure (e.g., sunburn and tanning) (16), therapeutic dose of nbUVB phototherapy (17, 18) and the development of skin cancers (19–22). Based on these differences, we concluded that there was a need to determine the carcinogenic effects of nbUVB treatment in patients with skin phototypes III–V.

TL-01 lamp-based nbUVB phototherapy is in widespread use in Korea and has shown great efficacy, especially in the treatment of psoriasis (17, 23). However, the photocarcinogenic risk of nbUVB in patients with skin phototypes III–V has not been established. Thus, this retrospective study was undertaken to compare the incidence of skin cancer in Korean patients with skin phototypes III–V treated with nbUVB with that in a control Korean population.

MATERIALS AND METHODS

Patients

The data analyzed in this retrospective study were collected from patients' medical records. Between March 1998 and June 2009, 445 patients with psoriasis, vitiligo, atopic dermatitis and other dermatoses received nbUVB phototherapy at Seoul National University (SNU) Hospital. Most patients were treated two or three times a week. Treatment began with an initial dose of 50–70% of the minimal erythemal dose (MED) followed by a 10–20%

Table I. *Skin cancer rates in Korea (2007)*

Skin cancer	Males	Females
Malignant melanoma (ICD-10 CD43)		
Crude rate per 100,000	0.8	0.8
Korean age-standardized rate per 100,000	0.7	0.5
Non-melanoma skin cancer (ICD-10 C44)		
Crude rate per 100,000	4.4	5.8
Korean age-standardized rate per 100,000	4.1	3.8

incremental dose regimen. During nbUVB phototherapy, patients received routine facial and genital protection. We reviewed patient medical records to obtain information on demographic characteristics, skin phototype, number of nbUVB sessions, total cumulative dose and other relevant items. Skin cancer diagnoses made since initial treatment with nbUVB were retrieved from the Korean Central Cancer Registry (see below for further details). The study was approved by the institutional review board of SNU Hospital.

Control population

The Annual Report of the National Cancer Registration and Statistics Program published by the Korea Ministry of Health and Welfare in December 2009 was used to compare data from Korean patients treated with nbUVB phototherapy with data from a control Korean population. This report is based on a nationwide, hospital-based cancer registry called the Korea Central Cancer Registry (KCCR), which integrates all data from national and regional cancer registries in Korea. Reported cancer cases were classified according to the International Classification of Diseases for Oncology 3rd edition and converted according to the International Classification of Diseases 10th edition (ICD-10).

According to the December 2009 report, the control population's crude incidence rate for melanoma was 0.8 cases per 100,000 person-years and the crude incidence rate for non-melanoma skin cancer (NMSC) 5.1 cases per 100,000 person-years (Table I).

Statistical analysis

Expected numbers of cases in the nbUVB-treated group and the standardized incidence ratios (SIRs) for melanoma and NMSC were calculated from the incidence rates in the control population. We assumed the presence of Poisson distribution in the skin tumor data. Statistical analyses were performed using SPSS version 17.0 (SPSS Inc. Chicago, IL, USA) and PAMCOMP version 1.41 (24).

RESULTS

Demographic data

Demographic data for the 445 patients who received at least one nbUVB phototherapy session between March 1998 and June 2009 are shown in Table II. Of these 445 patients, 358 (80.4%) suffered from psoriasis. Using the system for classifying skin phototypes suggested by Fitzpatrick (25), 52 patients were classified as having skin type III, 92 skin type IV and 40 skin type V. Skin type was not recorded for the remaining 261 patients.

Table II. *Summary of demographic parameters in patients undergoing narrowband UVB phototherapy at Seoul National University Hospital*

Parameter	Value
Number of patients	445
Age, years, mean ± SD	43.9 ± 16.0
Sex, M:F	253:192
Fitzpatrick's skin phototype	
III/IV/V	52/92/40
Not recorded	261

SD: standard deviation.

Table III. *Summary of the therapeutic parameters for narrowband UVB (nbUVB) and other phototherapies*

Parameter	Value
Number of treatments, mean (min–max)	33.6 (1–232)
Cumulative dose, J/cm^2, mean (min–max)	45.2 (0.1–354.6)
Follow-up period, months, mean (min–max)	34.4 (1–132)
Phototherapy other than nbUVB, *n* (%)	
PUVA therapy	36 (8.1)
Broadband UVB phototherapy	5 (1.1)

Narrowband UVB phototherapy

Among the 445 nbUVB patients, the average number of phototherapy sessions was 33.6 and the average cumulative dose of nbUVB 45.2 J/cm^2 (Table III). Seventeen patients received more than 100 nbUVB treatments (Fig. 1) and 9 patients more than 200 J/cm^2 of nbUVB irradiation (Fig. 2). The mean follow-up period was 34.4 months (maximum 132 months). Thirty-six patients (8.1%) had previously received PUVA treatment and 5 (1.1%) had undergone bbUVB treatment.

Development of skin cancer

In this study, patients treated with nbUVB were followed for 1,274 person-years. Numbers of expected cases in the nbUVB group were 0.010 for melanoma and 0.059 for NMSC, as calculated using the 2009 Annual Report of the Korean National Cancer Registration and Statistics Program with age-sex standardization.

Among the 445 nbUVB patients, no melanoma cases were reported during the follow-up period.

One case of BCC was observed, resulting in a non-significant increase in the SIR for NMSC [SIR 17.0;

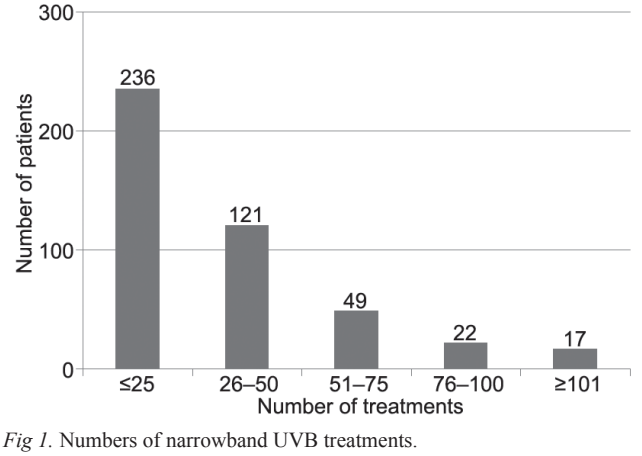

Fig 1. Numbers of narrowband UVB treatments.

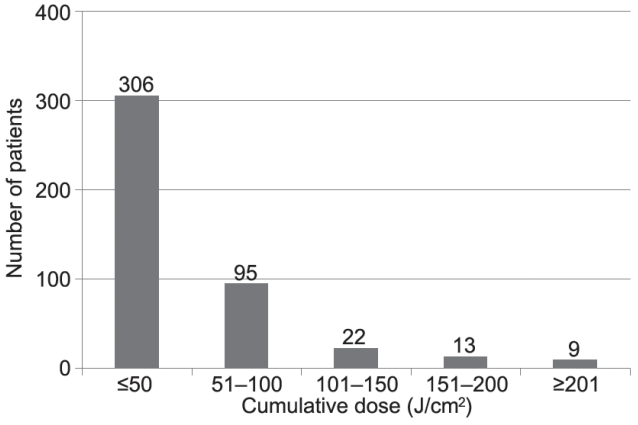

Fig 2. Cumulative doses of narrowband UVB phototherapy.

95% confidence interval (CI) 0.4–94.8]. The patient in question was a 52-year-old man who suffered from psoriasis and had received topical PUVA treatment before attending the SNU hospital for nbUVB treatment. A 4-mm diameter skin lesion was detected on the patient's leg in the 4th month (108 days) after the start of nbUVB phototherapy. However, the date of the lesion's onset was unknown. The lesion was histopathologically confirmed as a BCC and the patient's nbUVB phototherapy was stopped. Prior to the cessation of treatment, the patient had undergone 26 nbUVB sessions with a cumulative dose 42.4 J/cm^2.

DISCUSSION

In our retrospective study, the medical records of 445 patients treated with nbUVB phototherapy were reviewed. Although skin phototype was not recorded in all of the patients' records, we assumed that they all had type III, IV or V skin because they were all indigenous Koreans. The primary endpoint for each patient was the development of skin cancers during the follow-up period, which was a maximum of 11 years beginning in 1998. Skin tumors diagnosed before the start of nbUVB phototherapy were excluded.

Among the 445 patients whose records were analysed, no melanoma cases were observed. However, by day 108 of nbUVB treatment, one patient had developed a 4-mm-diameter BCC on his leg. Unfortunately, the date of the BCC's onset was unknown. However, it seems unlikely that the BCC developed as a result of nbUVB phototherapy, since the median increase in BCC diameter is only 0.5 mm over an average of 70 days (26). In addition, Hearn et al. (15) reported that tumors recorded within the first 6 months after the start of nbUVB therapy have usually been diagnosed by the time of referral for therapy. Aside from this one patient, none of the remaining 444 patients included in our study developed cancer during or after nbUVB therapy

The patient who developed a BCC had a previously received PUVA photochemotherapy in another hospital (although the number of treatments and the cumulative dose are unknown). This supports other reports that suggest that BCC can be induced by the synergic effects of UVB and PUVA. Lim & Stern (27) reported that exposure to high levels of UVB increased the risk of NMSC in PUVA-treated patients with type I or II skin. Also, in a study of 3,867 Scottish patients (15), there was a modest, but significant, increase in the incidence of BCC among patients treated with both nbUVB and PUVA. As an increased risk of NMSC following long-term PUVA therapy has not been reported in Asian patients (28), it remains to be determined whether nbUVB phototherapy increases skin cancer risk in patients with skin phototypes III–V who have previously been treated with PUVA. A further study is needed to compare the incidence of skin cancer between patients treated only with nbUVB and those treated with both PUVA and nbUVB.

Our study has certain limitations. If nbUVB does increase skin cancer risk, that might be related to the number of exposures and cumulative dose. However, only a few patients in our study had received large numbers of treatments and high cumulative doses. Furthermore, the mean follow-up period was short. A much longer follow-up period is desirable because there may be a lag of many years before skin cancers develop. In fact, studies looking for associations between nbUVB and skin cancer are very difficult to perform because of the need for a large number of subjects and a long follow-up period. Diffey & Farr (29) suggested that 50,000 new patients per year would be required in order to detect a two-fold increase in NMSC risk (an increase that would be unacceptably high) within a 5-year follow-up period and with an 80% statistical power at the 5% significance level. These study difficulties are particularly serious in subjects with skin phototypes III–V, such as Koreans, because their rates of skin cancer are much lower than those in subjects with fairer skin. While a study of 126 German patients followed for 726 person-years presented a statistical power of 83% when detecting a 5–6 fold increase in the incidence of skin cancer (13), we estimate that a study of 2,500 Korean patients followed for 25,000 person-years would be needed to detect a similar increase with an 80% statistical power at the 5% significance level.

This retrospective study did not show a significant increase in skin cancer risk in Korean patients with skin phototypes III–V receiving nbUVB phototherapy. Although it has several limitations, its results suggest that nbUVB phototherapy is a safe therapeutic modality for Korean patients. Nevertheless, we continue to follow-up the patients in this study. Moreover, a multi-centre study involving international collaborations with other Asian countries, such as China and Japan, is being considered. Such an expanded study would be able to gather data from more patients over longer periods of time than

a Korea-only study, thus improving the interpretive breadth and statistical power of the results obtained.

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