Chapter

Anatomically Adjustable Device for Large-Area Photodynamic Therapy

Alessandra Keiko Lima Fujita, Daniel José Chianfrome, Vinicius Sigari Moreira, Anderson Luiz Zanchin, Priscila Fernanda Campos de Menezes and Vanderlei Salvador Bagnato

Abstract

The illumination system composed of LEDs is an anatomically adjustable device of high intensity that can be applied in different areas of the body. It can be applied in health care, as in the dermatological and esthetic treatments. The device improved the treatment of pathological diseases (e.g. actinic keratosis) since disseminated lesions were reached in a single application, thus reducing the time of the procedure and ensuring homogeneous light distribution. It was compared with a smaller and non-adjustable illumination device and evaluated in the treatment of actinic keratosis. The results showed its versatile application and a uniform adjustment to body curvatures.

Keywords: light-emitting diodes, anatomical LED system, photodynamic therapy, actinic keratosis

1. Introduction

Topical photodynamic therapy (PDT) using 5-aminolevulinic acid (ALA) and its variants as the methyl-aminolevulinate (MAL) is a well-established technique that requires a light source appropriate to a specific application, such as cancer types and precancerous lesions [1, 2]. ALA and its variants are the main precursors of protoporphyrin IX (PpIX), which is an endogenous photosensitizer (PS) and it is part of the heme biosynthesis pathway. PpIX selectively sensitizes the diseased cells, and when it is excited by light of a certain wavelength, interact with molecular oxygen producing reactive cytotoxic species, causing cells death by necrosis, apoptosis or autophagy. However, for PDT to work is required, a PS, the wavelength to excite the PS, and the molecular oxygen present in the tissue [3].

Lasers and light-emitting diodes (LEDs) are suitable light sources for PDT applications. But fiber-optic-lasers are more appropriate for light endoscopes device, or even for intraoperative cavities illumination. In general, illumination devices have light emitters of fixed geometry. An exception is the recently developed fabric-like material made with single-mode optical fibers adjustable to a specific application or anatomic site [4–6].

Several authors have reported PDT applications in dermatology for not only non-melanoma skin cancer but esthetic treatments [7–10]. Therefore, laser devices with optical fibers are not convenient, since large areas and anatomic sites must be considered.

On the other hand, Light Emitting Diodes (LEDs) are an alternative illumination system and can deliver the necessary intensities for PDT performance at lower costs. LED devices have already been used in PDT for the treatment of skin cancer and esthetic procedures [11–16], however, its field of illumination is limited and it is not anatomically adjustable to the body, which hampers the treatment of areas not reached by the light. Moreover, it is not effective for the treatment of large lesions located in the head, neck, legs, and arms, due to its non-conformability, which causes the illumination not to be homogenous. An example is the treatment of actinic keratosis (AK), which are lesions more likely to occur on the face and scalp due to high exposure to the sun [6–10].

The treatment of AK with photodynamic therapy requires illumination of the entire region at the same intensity. In this case, the anatomical device enables the use of the PDT procedure and optimizes the application time.

The topical application of the ALA prodrug and its derivatives in PDT can be used by several light sources, so long as the photosensitive agents are activated by the wavelengths. Because the PpIX accumulated by the application of the prodrug has absorption peaks in the Soret band and four minor peaks in the Q band, 510 nm, 545 nm, 580 nm, and 630 nm. Thus, blue light-emitting at 450 nm and red light-emitting at 630 nm from LED devices can be applied for the activation of PpIX. However, blue light penetrates superficial layers of the skin and red-light deeper layers of the skin [17–20].

Our main concern was to produce a flexible LED illumination system of high-power that operates at 450 ± 10 nm and 630 ± 10 nm wavelengths; therefore, the device was tested by engineers and in clinical applications (AKs treatment and esthetic dysfunctions) [20, 21].

2. Illumination systems: small, fixed and adjustable array

Figure 1a shows LINCE® (MMOptics, São Carlos, SP, Brazil) device, it is treatment system and comprised of a circular probe (on the left) with approximately 9.0 cm^2 area that emits at 630 nm ± 10; on the right, it is a diagnostic system, which emits at 405 ± 10 nm and collects the image of the protoporphyrin IX formation induced by a topical application of a precursor on the skin. **Figure 1b** displays a square illumination of LINCE® accessory in a 61 cm^2 area, with LEDs (light-emitting diodes) emitting at 630 ± 10 nm.

The system is recommended for small lesions, such as superficial or nodular Basal Cell Carcinoma (BCC). It was developed in the Brazilian Skin Cancer PDT program, currently, already it is used in the clinics. [1, 4, 13–15].

The device was designed for improving the large area attachment of LINCE® accessory and providing an extra accessory that can multiply the possibilities of the Clinical PDT treatment. It was developed in cooperation with MMOptics industry (São Carlos, SP, Brazil) and Technological Support Laboratory (São Carlos Institute of Physics, University of São Paulo, São Carlos, SP, Brazil) and assembled by rectangular modules (up to 10, in principle).

However, a version with 5 modules composing a 192 cm^2 area of illumination (**Figure 2a**) was employed in this study. It consists of five LEDs (Luxeon Rebel, Lumileds Company) boards, thus totaling 30 LEDs emitting at 630 ± 10 nm, and 25

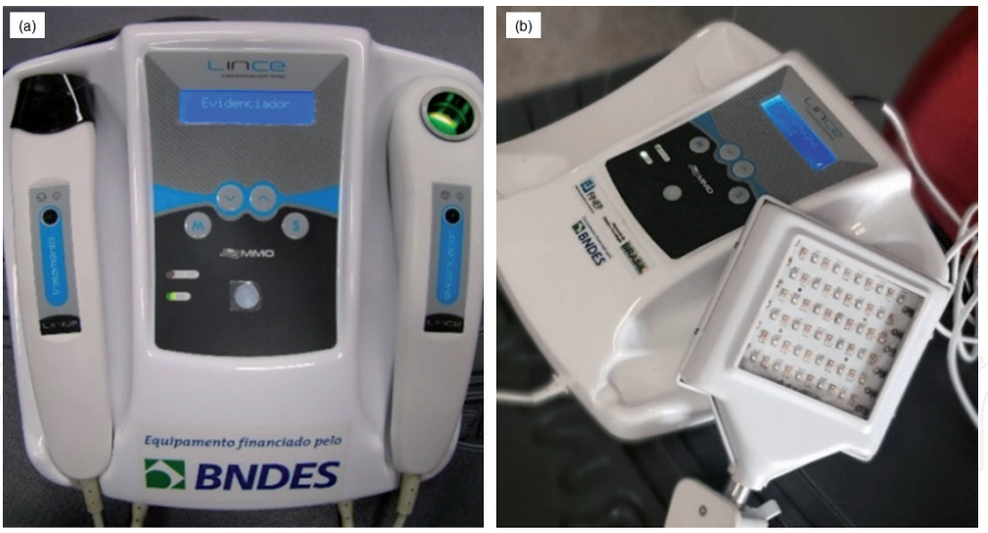

Figure 1.
(a) LINCE® equipment (MMOptics – Brazil): left - treatment system emitting at 630 nm; right - diagnostic system emitting at 405 ± 10 nm. (b) Square illumination of the LINCE® accessory emitting at 630 ± 10 nm.

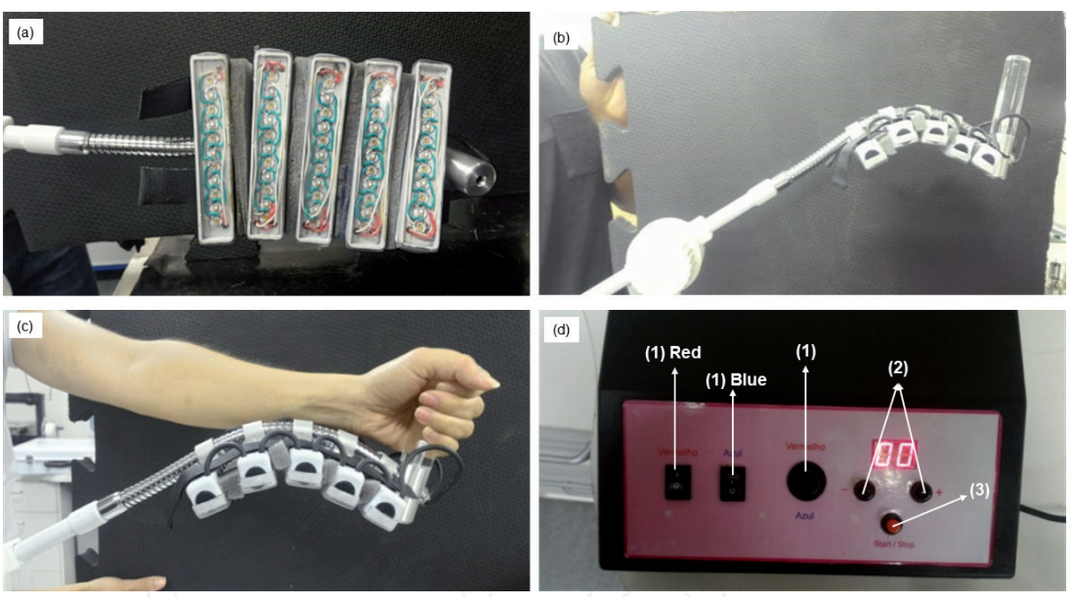

Figure 2.
Anatomically adjustable device. (a) Front of the equipment, where the LEDs are coupled and protected by plastic covers. (b) Side of the device, with an acrylic tube that facilitates its handling. (c) Adaptation of its curvature to the body by the acrylic tube. (d) Electronic box with the sequence of the drive buttons.

LEDs emitting at 450 ± 10 nm. A flexible tube was added for adapting the equipment to regions of the body (**Figure 2b**), and a handle facilitated its use in areas of curvature (**Figure 2c**) and avoided the bending of the plates with LEDs. Power sources of 16 V for emission at 450 ± 10 nm, and 5 V for emission at 630 ± 10 nm, both with 3 A electric current, are connected to the device. Below is the description of the power buttons (**Figure 2d**):

1. On/off button for the selection of the wavelength (450 nm or 630 nm).

2. Timer button for the selection of the illumination time in minutes.

3. Start/Stop button.

4. Button that turns on the equipment according to the wavelength selected (1).

5. Button that disables the equipment if pressed for a few seconds.

Figure 3 shows the way the equipment can be used in different parts of the body, according to an adequate anatomic configuration.

Figure 4 shows LINCE® (MMOptics, São Carlos, SP, Brazil) lighting system and its accessory (the 61 cm^2 fixed array) for the treatment of large areas. LINCE® is not adequate for treatments that require illumination of a larger area, since it does not have good applicability - it must be pushed away, which reduces the intensity and increases the application time. LINCE® accessory (the 61 cm^2 fixed array) has a larger area; however, it is fixed and does not fit the body anatomy. The delivered dose decreases when it moved away from the patient's skin, and a longer time is

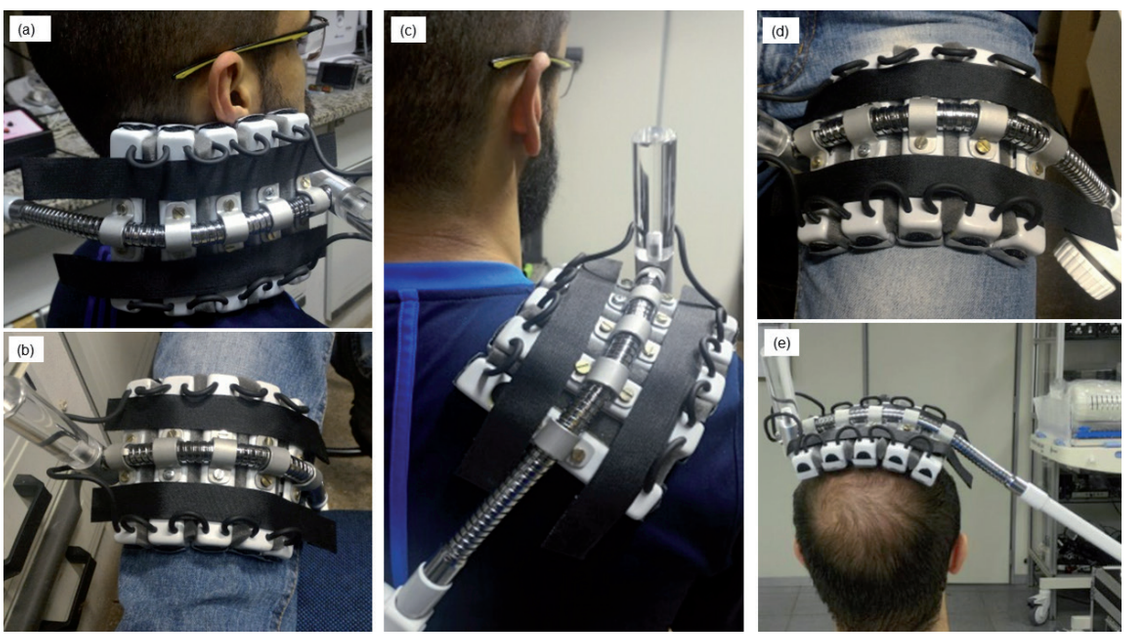

Figure 3.
Possible configurations of the device for different regions of the body. (a) Neck; (b) shin; (c) back; (d) quadriceps and (e) head.

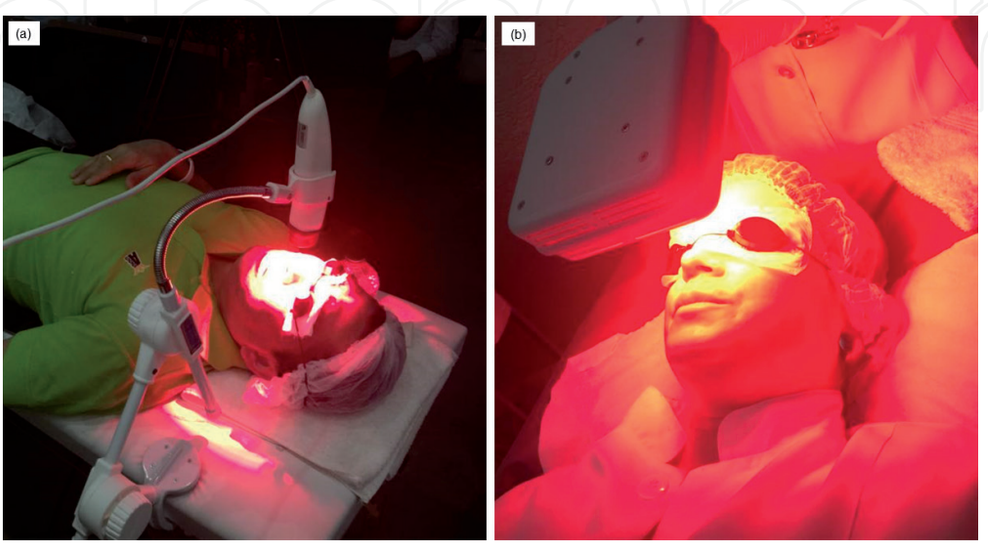

Figure 4.
Images of a treatment performed on the face. Devices emit at 630 nm. (a) LINCE® (MMOptics, São Carlos, SP, Brazil) - illumination system for treatment. (b) LINCE® accessory.

necessary for the achievement of the desired effect. In addition, the irradiance delivered on the target tissue is not homogeneous.

Figure 5 shows the PDT treatment for AK and acne vulgaris by the anatomical device.

AKs lesions often appear scattered in a specific region of the body most exposed to the sun. The device optimizes the PDT treatment so that it covers extensive regions and delivers the necessary intensity. **Figure 5a** shows the device used for the treatment of AKs at the back of the hand. The device enabled the treatment of both hands concomitantly. **Figure 5b** displays the device being used in patients with actinic keratosis on top of the head. The shape of the device adjusted to the anatomy of the region promotes uniform illumination and covers the entire area of lesions, thus reducing the number of exposures needed to treat larger areas effectively.

Figure 5c and **d** show the device being used for the treatment of acne vulgaris in the face. It was leaned against the treated area so that the desired intensity and fluency rate could be delivered. The equipment was moved a little away from the patient to allow a clearer photograph and the area treated. A flat device would not treat the surface so closely and uniformly.

2.1 Optical characteristics - adjustable array

The light distribution was measured using the laser power meter (LabMax-TOP, Coherent Inc., Santa Clara, USA). It has a 0.5 cm^2 circular area sensor and the wavelength was configured for the collection of the intensity measured. The light distribution was measured 5 cm away from the equipment, and the power meter

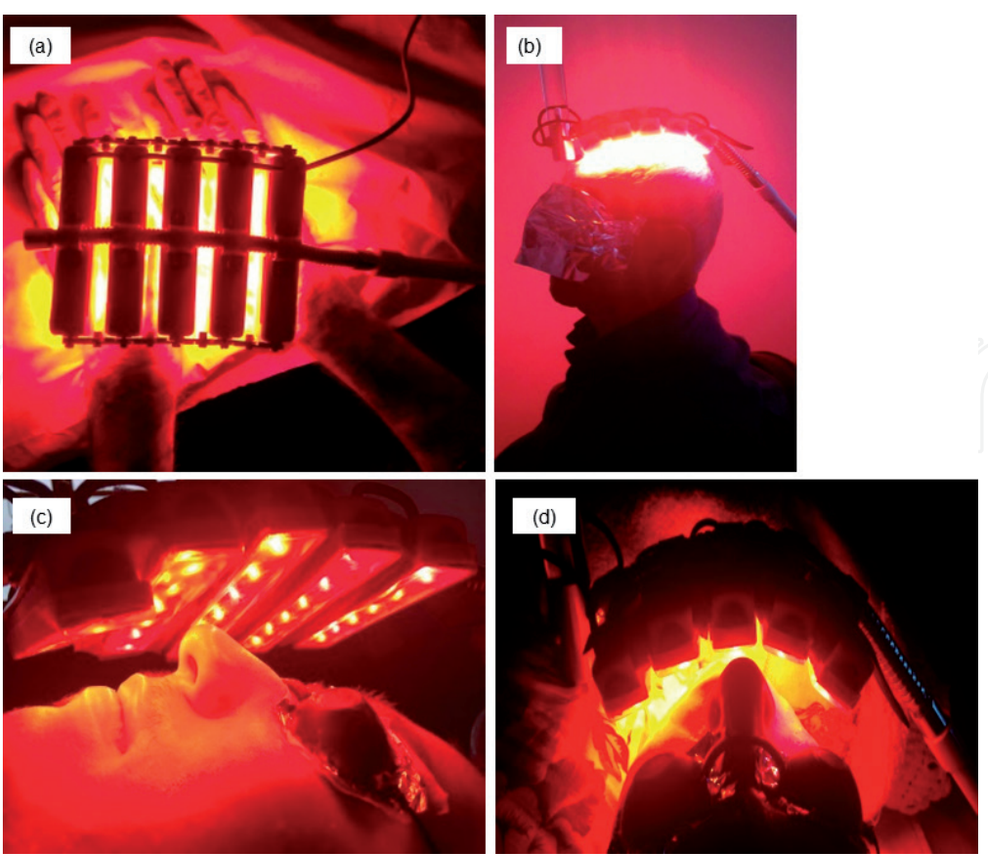

Figure 5.
(a) AK treatment with the anatomical device at the back of the hand. Both hands can be treated concomitantly. (b) AK treatment with the anatomical device in the head region, covering its whole region. (c) and (d) PDT procedure for acne vulgaris on the face.

sensor was scanned throughout the device area. The distance from each point collected was the diameter of the power meter detector.

Figure 6 shows the measurement of intensity (collected point to point) of the light emission of the anatomical device.

The device remained on for 20 minutes to perform the warm-up test, and it did not heat up, which has proven the light-emitting surface causes no thermal damage to the skin.

Planar irradiance distribution was mapped out at a range of distances from the light source. Measurements were collected from the distance zero until 5 cm of the laser power meter, varying each 1 cm (**Figure 7**). The covered area of the measurements corresponds to 192 cm^2 (13 × 15 cm). The intensity fluctuates with a small decay at the boundary for both wavelengths. We calculated the average intensity, considering a continuous emitting surface (**Figure 8**). The intensity at any z-axis from the emitting surface can be evaluated through the integration of all elementary emitters.

To calculate the intensity at a certain position (x, y, z) above the surface, we can proceed with the sum of the contributions of all the emitters distributed on the surface. Imagine that in each position determined by the coordinates (x', y') there is an emitting element. The contribution of all of them to the intensity at the point

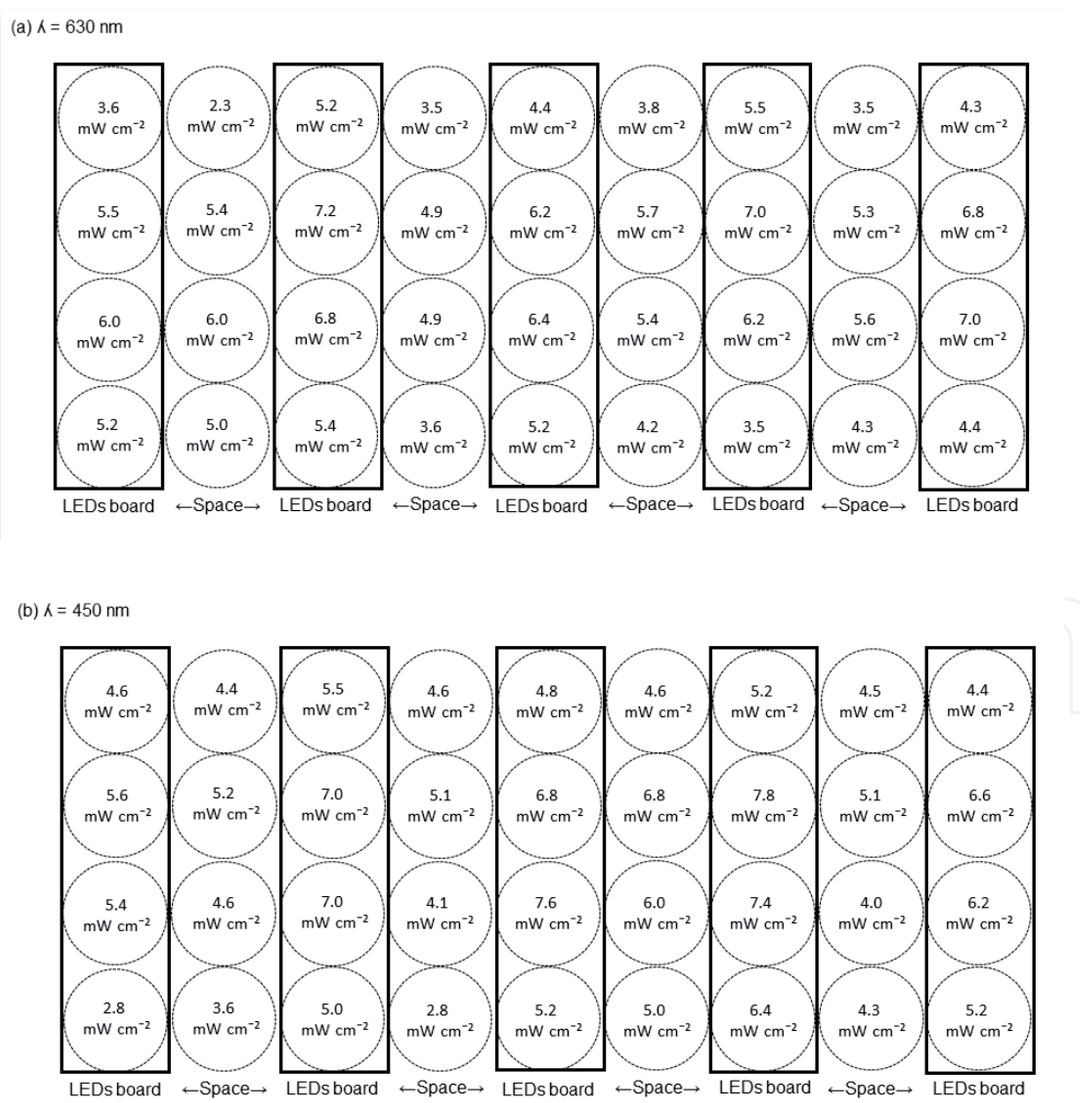

Figure 6.
Intensity measurements were collected from point to point in the anatomical device area. (a) Intensity emitting at 630 ± 10 nm and (b) intensity emitting at 450 ± 10 nm.

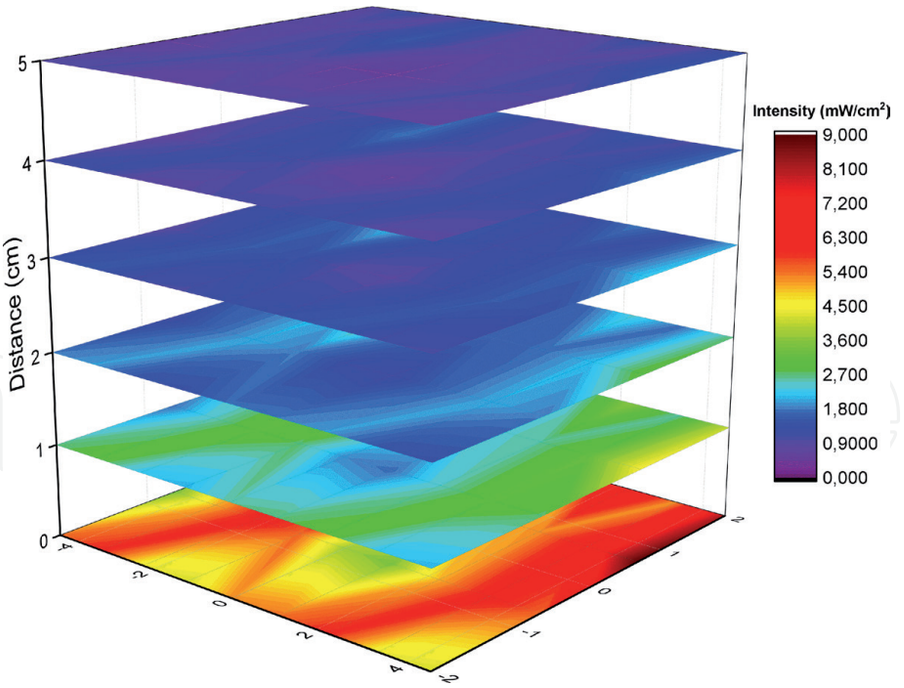

Figure 7.
Intensity versus distance. The intensity was measured by LabMax-TOP laser power meter (Coherent Inc., Santa Clara, USA). Measurements were collected every 1 cm from the device up to 5 cm and scanned throughout the device area.

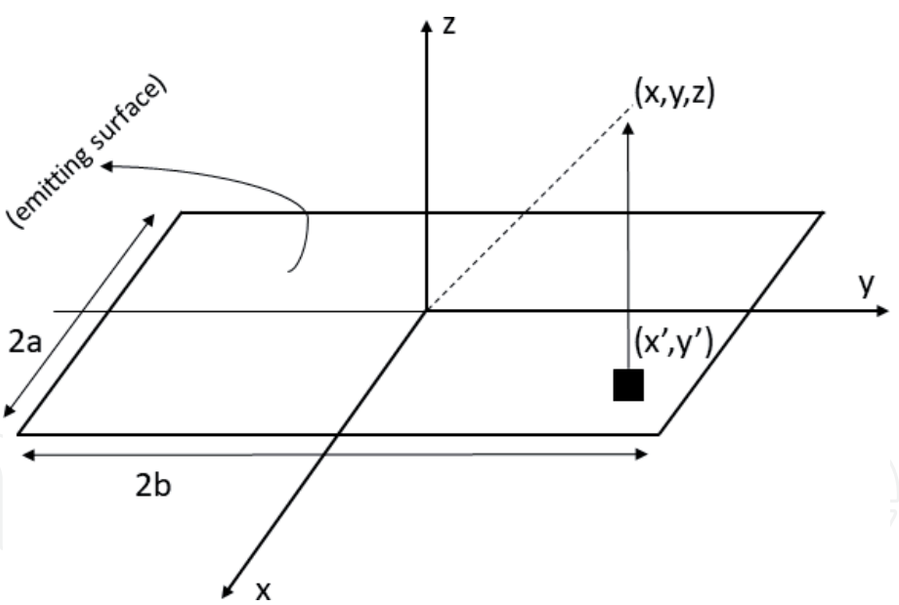

Figure 8.
Average intensity calculated by the integral of the elementary emitters at any point of the intensity (x′,y′).

outside the surface (x, y, z) is then given by the integral of all elements, covering the entire area that contains emitters. Considering as in **Figure 8**, where we represent in a simplified way the position of the issuer and the point considered, we have the integral:

$$I(x,y,z) = Io \iint_{al\ surface} \frac{dx'dy'}{(x-x')^2 + (y-y')^2 + z^2} \tag{1}$$

If we consider a special point of interest, the central point of the distribution (x = 0 and y = 0), we have that the previous integral is reduced to:

$$I(z) = Io \iint_{al\ surface} \frac{dx'dy'}{x^2 + y^2 + z^2} \tag{2}$$

If I_0 is close to the emitters intensity ($z \to 0$), the intensity at point (x, y, z) is given by (3)

$$I(x,y,z) = I_0 \int_{-a-b}^{+a+b}\int \frac{dx'dy'}{(x-x')^2 + (y-y')^2 + (z-z')^{2.}}$$

At the center of the illuminating area (x = y = 0), at any distance z

$$I(z) = I_0 \int_{-a-b}^{+a+b}\int \frac{dx'dy'}{x'^2 + y'^2 + z'^2} \tag{4}$$

The integral can be solved by traditional approximation and results in a center average intensity of

$$I(z) = \pi I_0 \ln\left(\frac{\frac{4ab}{\pi} + z^2}{z^2}\right) \tag{5}$$

The calibration of I_0 at certain z provides a center intensity at a distance z from the device shown in **Figure 9**.

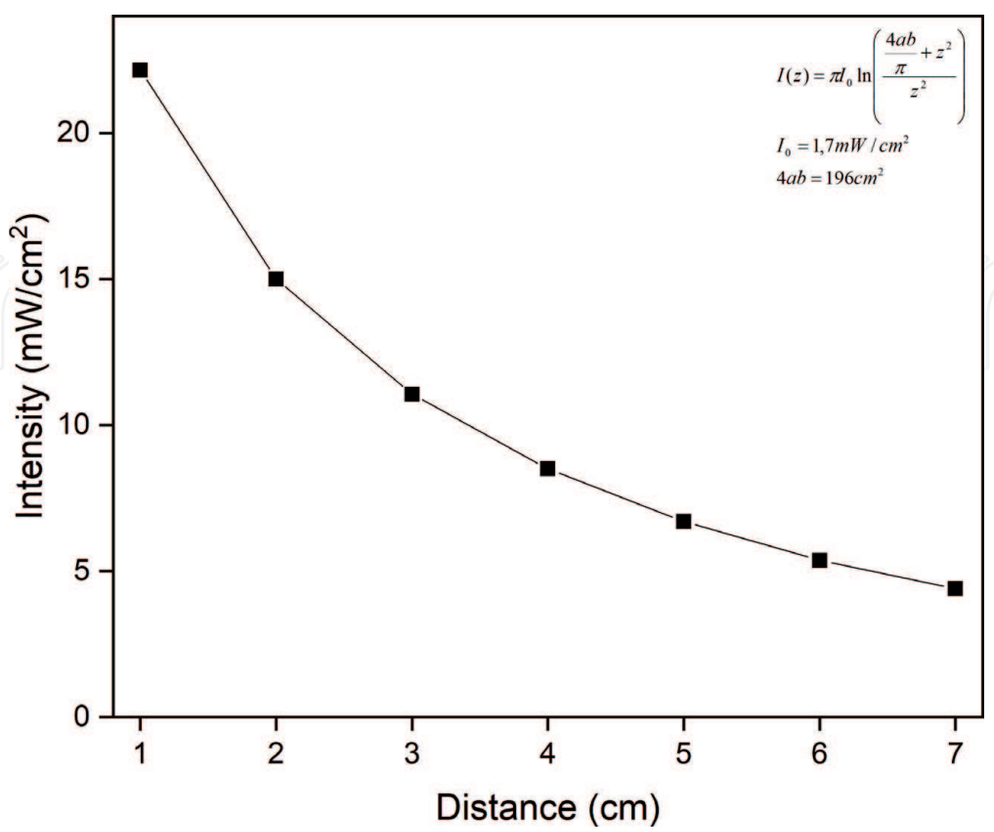

Figure 9.
Intensity decay caused by an increase in the distance from the device to the target tissue.

The ideal distance for the treatment is up to 1 cm because since the presence of the emitter is dominant in this distance, the intensity fluctuates. Therefore, if the expected average is considered the center intensity, the dose can be obtained from **Figure 9**, and for each 1 s illumination, the intensity (mW/cm^2) corresponds to the 10^{-3} J/cm^2 total dose delivered. At a 1 cm distance, the total dose delivery is 1.32 J/cm^2 energy, while at 5 cm distance, it decays to 0.39 J/cm^2.

Generally, the total dose applied in the PDT procedures ranges from 30 to 100 J/cm^2, so that for device equates a 22 to 66-minute application time, respectively. This time increases if the illumination distance increases. Those times are equivalent to 450 ± 10 nm and 630 ± 10 nm emissions.

3. Clinical demonstration: anatomical device (adjustable array)

LINCE® accessory (fixed array) and the anatomical device (adjustable array) were designed towards meeting the clinical needs for the PDT application in the AK treatment. However, esthetics and rehabilitation procedures that use low-power laser have been intensively studied, and more versatile devices with larger illumination areas have attracted more health professionals. The development of a device that enables the choice of wavelength is fundamental for the adoption of the appropriate procedure for a given treatment.

Two patients with a clinical diagnosis of AK were recruited to be treated with PDT using the anatomical device (**Figure 10**). The protocol applied was ALA-20% cream; incubation time 1 h 30 min; total dose 50 J/cm^2, emission at 630 ± 10 nm. After one month, no residual lesion was observed in the nose; the scalp region showed a residual lesion, which indicates an 85% elimination.

The anatomical device (adjustable array) was able to cover all extension of the lesions treated on the nose and scalp. The emission surface was leaning against the treatment region and there was no heating, which enabled the delivery of the adequate intensity.

LINCE® accessory (the 61 cm^2 fixed array) was observed that excessive heating occurred when applied in contact with the treatment area, causing greater

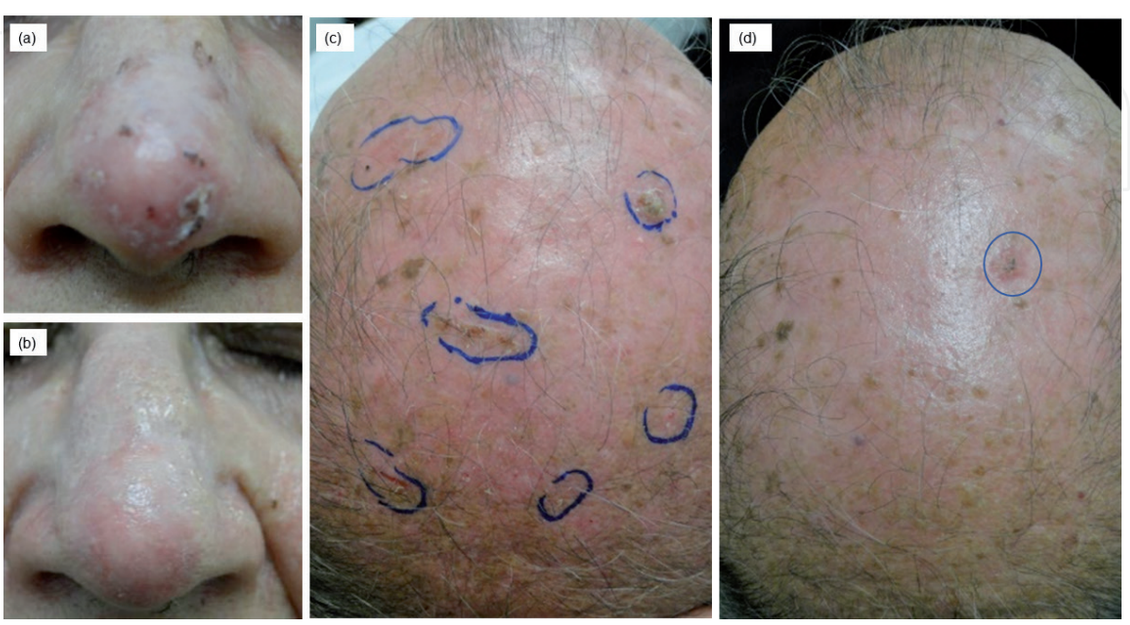

Figure 10.
(a) AK lesion on the nose. (b) 30 days after the PDT procedure - no residual lesion. (c) Approximately six AKs lesions scattered on the scalp region. (d) 30 days after the PDT procedure - a residual lesion.

discomfort to the patient. This is due to its geometry of heat dissipation because it has more LEDs per area than the anatomical device (192 cm^2 adjustable array). In the anatomical device, the LEDs are divided between the boards, thus obtaining a better air circulation mechanism and more heat dissipation. Therefore, the anatomical device is more comfortable for the patient and it is possible to apply it in contact with the treated area and operating at high intensity without causing excessive heating.

4. Conclusion

LINCE® (MMOptics, São Carlos, SP, Brazil) device has become excellent commercial equipment for the PDT treatment for non-melanoma skin cancer in Brazil. Thereby, the development of an anatomical device with a larger illumination area becomes more efficient to treat extensive lesions.

The anatomical device was designed to optimize the PDT procedure in AK lesions scattered in a specific region of the body and in body sites, where a machine is required for the obtaining of the curvature according to the anatomy of the treated region. The device treated extensive lesions and reached their entire extension. It suffered no heating during treatments, therefore the thermal energy dissipation in this shape was more effective, and caused no sensation of thermal discomfort to the patient.

The anatomical device can be used for several dermatological clinical applications, including esthetic procedures for facial, body, and capillary treatments.

Further clinical tests will be conducted and, if necessary, the device will undergo modifications towards improvements in clinical procedures.

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Conflict of interest

The author Anderson Luiz Zanchin is employee at MMOptics Ltda.

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