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Review Article

Targeted Phototherapy (newer phototherapy)

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ABSTRACT

Conventional phototherapy uses a whole body cabinet or body part machine such as hand, foot or scalp machines. They have many disadvantages due to which new phototherapy technique was then developed to overcome this situation. This new technique is called targeted phototherapy which includes excimer laser, intense pulse light system (IPL), photodynamic therapy and ultraviolet (UV) light source with a sophisticated delivery system which is easy to be operated by hands. The mechanisms of action of targeted phototherapy systems are similar to those in conventional UVB/UVA therapy. They have many advantages like less chances of side effects, avoidance of exposure of unnecessary sites, faster response, shortening of the duration of treatments. But they have disadvantages like high costs and inability to use for extensive areas. This review article discusses targeted phototherapy in considerable to the mechanism of actions and advantages and disadvantages in comparison to the conventional phototherapy.

Keywords: Conventional phototherapy; targeted phototherapy; excimer laser; intense pulse light system (IPL); photodynamic therapy; ultraviolet (UV) light

INTRODUCTION

Phototherapy is a therapeutic strategy in dermatology for treating several skin diseases. Conventional phototherapy uses a whole body cabinet or body part machine such as hand, foot or scalp machines [1,2]. It includes Broadband UVB therapy, Ultraviolet A (UVA) therapy, SUP or selective ultraviolet phototherapy (310-318) therapy, Narrowband UVB (311 nm). Ultraviolet A1(UVA1) therapy Phototherapy is used for a wide variety of skin diseases. There has been considerable progress in cellular and cutaneous photobiology leading to improved understanding of different photodermatoses and their treatment. However, the developments in phototherapy have been comparatively slow, as reflected in a recent publication that "developments in phototherapy have not kept pace with scientific progress, as has been the case with radiotherapy" [3].

The conventional phototherapy have many disadvantages like exposing uninvolved areas, slow delivery system and lengthy treatment sessions, multiple and frequent visits to clinic, difficulty in treating certain areas (such as genitalia, oral mucosa, ear, etc.), difficulty in treating children who may feel intimidated by the large machines, large office space required to house the bulky machines [4]. Due to those disadvantages of conventional phototherapy, a new phototherapy technique was then developed to overcome these situations. This technique was called targeted phototherapy or also known as concentrated phototherapy, focused phototherapy, micro phototherapy and localized phototherapy. This review mainly focussed on this newer technique called targeted phototherapy.

Targeted phototherapy is defined as a therapeutic method using a device that delivers laser light or ultraviolet light spectrum of a specific wavelength focused on specific body areas or lesions. This definition includes different technologies used such as excimer laser, intense pulse light system (IPL), photodynamic therapy, and ultraviolet (UV) light source with a sophisticated delivery system which is easy to be operated by hands [3].

MECHANISM OF ACTIONS

Most targeted phototherapy devices (laser or non-laser type) emit radiation in the UVB range with

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peak emission in the narrowband wavelength (around 308-311 nm), while some light-based non laser machines emit UVA radiation also. Hence mechanisms of action of targeted phototherapy systems are similar to those in conventional UVB/UVA therapy [2,5-8]. Ultraviolet light has a spectrum which is divided into 3 parts according to their wavelengths, namely UVC with the shortest wavelength (200-290 nm), UVB with the intermediate wavelength (290-320 nm) and UVA with the longest wavelength (320 -400 nm). UVA is then divided into UVA1 (340-400 nm) and UVA2 (320-340 nm)[9,10]. The light sources include broadband UVB (BB-UVB) with a wavelength of 290-320 and a peak at 313 nm, narrowband UVB (NB-UVB) with a wavelength of 311-313 nm, UVA (320-400 nm, peaks at 355 nm) and UVA1 (340-400 nm, peaks at 365 nm). Excimer laser which emits monochromatic UV light has various wavelength ranges depending on the molecules used, especially in the field of dermatology XeCl laser with a wavelength of 308 nm. Various mechanisms were found and it was proposed that phototherapy can give either in systemic or local effect. Ultraviolet B rays have shorter wavelengths so that they do not penetrate as deeply as UVA rays do, but UVB rays have more energy. Ultraviolet B phototherapy primer effect is on the function of keratinocytes and Langerhans cells. The effectiveness of UVB therapy in psoriasis especially lies on its anti proliferative effects. The decrease of pruritus after the treatment with both BB-UVB and NB-UVB is caused by cell mast apoptosis [11]. In the use of targeted BB UVB phototherapy, NB UVB and excimer laser, T cell apoptosis was found [12-14]. The apoptosis mechanism may be caused by the damage of the epidermis and dermis cells which are susceptible to UV light exposure. Ultraviolet B rays cause DNA damage and formation of pyrimidine dimer [15]. In addition to T cell apoptosis, UVB radiation triggers changes in cytokine production, local immunosuppression, stimulation of melanocyte-stimulating hormone (MSH), increases migration, proliferation of melanocytes and melanogenesis [16,17]. A two-step effect of NBUVB has been proposed – both of them may occur simultaneously although. Firstly, there is immunomodulation (local as well as systemic), leading to down regulation of immune attack against the melanocytes. Subsequently, the melanocytes are stimulated to migrate to the epidermis and synthesize melanin [18]. NBUVB phototherapy increases synthesis of IL-1, TNF-α and LTC-4 and these cytokines induce melanocyte mitogenesis, melanogenesis and melanocyte migration. However, the roles of IL-1 and TNF-α in melanogenesis are controversial and contradictory, as has been observed in some studies. It was proposed that TNF-α inhibits the expression and activity of tyrosinase, the key enzyme in melanin synthesis. This inhibition of melanogenesis induced by TNF-α is secondary to activation of nuclear-factor κB [19]. IL-1 stimulates synthesis of endothelin-1, which is mitogenic and melanogenic. The contradiction is that IL-1β has been found to decrease proliferation of melanocytes and melanogenesis, while IL-1β decreases melanocyte tyrosinase activity without any effect on proliferation [20]. It was also observed that the increase of expression of endothelin-1, IL-1 and tyrosinase in human keratinocytes *in vivo* and *in vitro* after UVB irradiation suggested the possible mechanism of repigmentation [21]. Release of prostaglandins (PGE_2 and PGF_2) is another mechanism of action of phototherapy [22]. PGE_2 is synthesized in the skin and regulates melanocyte and Langerhans cell function, and promotes melanocyte mitogenesis [23]. Ultraviolet A has a longer wavelength, so it can reach the dermis and have an effect on fibroblasts, dermal dendritic cells, endothelial cells, T lymphocytes in the dermis and granulocytes. In atopic dermatitis, UVA is shown to cause apoptosis of T helper cells in the skin with eczema lesions through FAS/FAS ligand system [24]. In addition, UVA and UVA1 irradiation may also decrease histamine release by basophils and mast cells [25]. The combination between UVA and psoralen (PUVA) has a more complex mechanism. Psoralen undergoes intercalation in the double-stranded DNA. Ultraviolet A exposure causes the formation of 3,4 or 4',5' cyclobutane mono adduct with pyrimidine bases on a single photon absorption. The double helix DNA then undergoes a cross linking process when the absorbed second light photon by 2monoadducts forming a bifunctional adduct. DNA replication is inhibited by the cross-linking results in cell cycle disruption and decreased epidermal proliferation. Once psoralen excited by the photons, it can react with oxygen molecules to form reactive oxygen species (ROS),which can cause mitochondrial dysfunction and apoptosis of Langerhans cells, keratinocytes and lymphocytes. Both UVA and UVB cause decreased expression of ICAM-1 and increased levels of immunosuppressive cis-urocanic acid that it can depress cellular immune response and inhibit Langerhans cells activities [26]. Although the mechanism of action of targeted phototherapy is similar to the mechanism of action of conventional UVB/UVA phototherapy, it is thought to be more aggressive because the dose given can be higher than

the erythemogenic dose, which results in a greater efficacy due to its ability to deliver the energy to the deeper dermis layer [27-33].

Advantages [30]

Several advantages have been claimed for targeted phototherapy: Exposure of involved areas only and sparing of uninvolved areas, thus minimizing acute side effects such as erythema and long-term risk of skin cancer over unaffected skin; quick delivery of energy and thereby shortened duration of treatment; delivery of higher doses (super-erythemogenic doses) of energy because uninvolved areas are not exposed, higher doses of energy can be delivered selectively to the lesions, thereby enhancing efficacy and achieving faster response; shortening of duration of treatment, leading to less frequent visits to clinic and is more convenient for the patient; the maneuverable hand piece allows treatment of difficult areas such as scalp, nose, genitals, oral mucosa, ear, etc; easy administration for children as delivery is hand-held and it also occupies less space.

Disadvantages [30,31]

Targeted phototherapy devices have certain disadvantages; they are more expensive. Also, they are not adequate to treat extensive areas in view of the cost of treatment and time involved in treatment. They are not recommended for use if lesions occur over more than 10% of the body area.

CONVENTIONAL PHOTOTHERAPY

Scherschun, et al retrospectively analyzed their experience of treating vitiligo with NB-UVB administered as monotherapy 3 times a week [34]. Five of their seven patients achieved more than 75% repigmentation with a mean of 19 treatments, whereas the remaining two patients had 50% and 40% repigmentation after 46 and 48 treatments respectively. In a recent meta-analysis of non-surgical therapies in generalized vitiligo by Njoo, et al [35] higher success rates were observed with NB-UVB (63%) than with oral PUVA (51%). As in the western population, NB-UVB phototherapy produces a cosmetically good color match in Indian patient [36]. Its distinct advantages over PUVA include the lack of psoralen related side effects and precautions, cosmetically better color match, and its safety in children. However, the relative stability of NB-UVB induced repigmentation over PUVA, its maximum safe duration and cumulative dose allowed still remain to be determined.

The NB-UVB lamp was developed as a 'new' UVB phototherapy source with an emission spectrum within the therapeutic waveband for psoriasis phototherapy. NB-UVB phototherapy has a higher ratio of therapeutic to erythemogenic activity, resulting in increased efficacy, reduced incidence of burning and longer remission. Results from two therapeutic action spectroscopy studies indicated that wavelengths of the range 295-320 nm are effective in clearing psoriasis, whereas shorter wavelengths are more erythemogenic and wavelengths longer than 320 are less therapeutic [37,38]. Subsequent clinical studies have tended to report significantly greater improvement of psoriasis with NB-UVB including reduced incidence of burning episodes, increased efficacy and longer remission when compared with broad band sources [39]. When NB-UVB phototherapy and PUVA were compared, there was little overall difference in efficacy [40,41].

Prophylactic low dose NB-UVB has been found to be useful in various predominantly UVA induced photosensitivity disorders like polymorphic light eruption, actinic prurigo, hydroa vacciniforme and the cutaneous porphyrias by providing a 'hardening photoprotective' effect. A typical course involves 10-15 treatments given in early spring [42]. We have also observed a beneficial role of NB-UVB in patients with airborne contact dermatitis to Parthenium hysterophorus, a frustrating problem for both the patient and the physician [43].

NEWER/TARGETTED PHOTOTHERAPY

Excimer laser/excimer light (308 nm)

The various uses of Excimer laser include palmoplantar pustular psoriasis, plaque-type psoriasis, nail psoriasis, chronic atopic dermatitis of the hands, non-atopic dermatitis of the hands and alopecia areata. The common side-effects include intense erythema and, more rarely, blisters, but these were are usually well tolerated [32].

Steven Paul Nisticò M.D., Rosita Saraceno M.D., Caterina Schipani M.D, et al (2009) showed different applications of Monochromatic Excimer Light in skin diseases on 152 patients with stable and localized plaque psoriasis, 47 with palmoplantar psoriasis, 7 with palmoplantar pustulosis, 32 with vitiligo, 11 with prurigo nodularis, 9 with mycosis fungoides

stage Ia, 8 with alopecia, 5 with localized scleroderma, 5 with genital lichen sclerosus, and 3 with granuloma annulare showed complete remission in more than 50% of patients with plaque psoriasis and palmoplantar dermatoses, respectively, complete remission in all patients affected by mycosis fungoides, excellent repigmentation in one third of vitiligo patients, hair re growth in three patients with alopecia areata, an overall improvement in prurigo nodularis, a partial remission in patients affected by localized scleroderma and a complete remission in most of the patients with genital lichen sclerosus and granuloma annular [33].

DUALIGHT

(Previously called Theralight) emits both UVA radiation in the range 330-380 nm and UVB in the range 290-330 nm with peak at 303 nm [5]. The system has a 2-meter long fiber-optic delivery system with a spot size of 4 cm^2. UVA intensity is 10-550 mW/cm^2 for 3.63-cm^2 exit aperture, while UVB intensity is 50-250 mW/cm^2 for 3.63-cm^2 exit aperture.

B CLEAR TARGETTED PHTOCLEARING SYSTEM

B clear system is mercury-based noncoherent UVB radiation with a therapeutic wavelength of 290 to 320 nm and pulse width of 0.5 to 2.0 seconds. Fluence ranges from 50 to 800 mJ/cm^2 in increments of 10 mJ/cm^2. Its disadvantage is that only UVB range is available, unlike Dualight, which delivers both UVA and UVB ranges [2,44].

PHOTODYNAMIC THERAPY

Photodynamic therapy (PDT) involves the use of photochemical reactions mediated through the interaction of photosensitizing agents, light and oxygen for the treatment of malignant or benign diseases. Photodynamic therapy is a 2-step procedure. In the first step, the photosensitizer is administered to the patient by one of several routes (eg, topical, oral, intravenous) and it is allowed to be taken up by the target cells. The second step involves the activation of the photosensitizer in the presence of oxygen with a specific wavelength of light directed toward the target tissue. Then, sunburn reaction will occur which usually heals by 4-8 weeks. Because the photosensitizer is preferentially absorbed by hyperproliferative tissue and the light source is directly targeted on the lesional tissue, photodynamic therapy achieves dual selectivity, minimizing damage to adjacent healthy structures. The photosensitizers are aminolevulinic acid (ALA) and methyl aminolevulinate (MAL), Porfimer sodium (Photofrin™), Benzoporphyrin derivative monacid ring A, Tin ethyl etioporphyrin, Lutetium texaphyrin [45-48].

Light at a wavelength corresponding to a peak of the porphyrin excitation spectrum in tissues is used to most efficiently generate a therapeutic effect. The Soret band (approximately 405-420 nm) is the most important excitation peak of protoporphyrin IX and is included in the spectral output of the US Food and Drug Administration (FDA)– approved Blu-U device, which is used with ALA. Another peak in the excitation spectrum of porphyrins includes a red peak at approximately 635 nm, which is targeted by different devices, including those approved to be used with MAL [34,36-38].

Light sources used in PDT include laser or non laser light. Laser light has the advantages of being [45]:

- monochromatic (exactly one colour/wavelength that corresponds with the peak absorption of the photosensitising agent)
- coherent (able to focus light waves to specific site)
- intense (high irradiance allowing for shorter treatment times)

The only FDA-approved indication for ALA photodynamic therapy (PDT) and MAL photodynamic therapy in dermatology is currently the treatment of AKs. Common off-label uses include the treatment of BCC, photoaging, acne vulgaris, and Bowen disease [49-51].

Side effects from PDT are due to the treated area being sensitive to light. The photosensitivity usually lasts about 24 hours (depending on the specific agent). Side effects may include [45]:

- Burning/stinging sensation
- Swelling and redness
- Crusting
- Itchiness
- Peeling and blisters
- Skin infections

The treated area should be protected from light exposure using a dressing. A local anaesthetic such as lignocaine (lidocaine) spray may be applied to

the treatment area before or during Stage 2 of the procedure to help relieve pain [52].

The author experience is, although excimer light is effective for treatment of stable localised vitiligo and psoriasis, its efficacy is limited for treatment of alopecia areata.

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