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Ultraviolet radiation therapy in wound healing - an orientation paper

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ABSTRACT

In terms of the International Classification of Functioning, Disability and Health the speed and the success of the wound healing process depends on a series of personal factors and environmental factors. New therapeutical approaches are needed regarding wound healing, approaches answering the following requirements: low level of toxicity and reduced risk of side and systemic effects, minimal invasivity, high cost-efficiency.

Objectives: The main objective of this paper is to profile a most complete picture of the utility of ultraviolet therapy in wound care, from nowadays perspectives.

Material and Method: Bibliographic research on the Internet for reviews, journal articles and clinical guidelines regarding recent advances in ultraviolet therapy for wound healing.

Outcomes: The evidence sustaining the benefits of ultraviolet therapy in wound healing comes from a number of animal model experiments and a few clinical studies.

Conclusions: UVA, UVB and UVC seem to act by influencing cell signaling and by inducing changes in the cell metabolism and proliferation (biostimulation), inducing and sustaining wound healing. UVC act also by antibacterial effect. There are some issues to be managed in the future, in order to ensure safe use of UV in wound care.

Key words: ultraviolet therapy, wound healing, wound care

INTRODUCTION

Wound healing is a complex process consisting on coordinated local and systemic mechanisms involving different types of cells and tissues, and comprising a series of phases, in a specific sequence. In terms of the International Classification of Functioning, Disability and Health, known more commonly as ICF, the speed and the success of the wound healing process

depends on a series of a) personal factors (age, nutritional status, cardio-vascular, endocrine and metabolic comorbidities, infections, immune system functionality, psychological condition, physical activity level) and b) environmental factors (level of daily exposure to natural physical factors, environmental conditions regarding home, working place, means of transportation, hospital conditions etc). Impaired wound healing, in its turn, creates physical and psychological distress, closing a vicious circle (1).

Wound care is an important medical issue, due also to the following contextual factors: a) increasing rate of surviving traumatic events, b) the ageing population with chronic associated comorbidities, c) increasing risk of infection in the age of immunologic impairments and of germs resistant to antibiotics. New therapeutical approaches are needed regarding wound healing, approaches answering the following requirements: low level of toxicity and reduced risk of side effects, minimal invasivity, higher cost-efficiency. Several studies indicate the beneficial effects in wound healing of the different applications of phototherapy, including ultraviolet radiations applications.

Despite the reduced potential to penetrate the human skin, the ultraviolet radiation induces several important biological and physiological effects, alongside the visible and the infrared radiations of the solar optical emission spectrum. The effects depend on the radiation wavelength, dose – the quantity of energy used for the radiation exposure, and the UV source (2, 3).

Objectives

After a period of neglect, the general interest regarding ultraviolet therapy is renewed nowadays. The advances in investigations technology allow us to decipher the mechanisms of action of the ultraviolet radiation, as well as to assess the complex local and systemic effects of the different segments of the ultraviolet spectrum.

Searching PubMed Central® at National Center for Biotechnology Information (PMC NCBI) for the publications containing the terms “ultraviolet” and “wound healing” or “ultraviolet and pressure ulcer” in their abstract, we found as follows:

a) Published Date from 1995/03/27 to 2005/03/27, Added to PMC Date from 1995/03/27 to 2005/03/27. Results: 5
b) Published in the last 10 years, Added to PMC in the last 10 years (from 2005/03/31 to 2015/03/28). Results: 241, from which, 191 are published in the last 5 years.

The main objective of this paper is to profile a comprehensive picture of the utility of ultraviolet therapy in wound healing, from nowadays perspectives.

MATERIAL AND METHOD

Search on the Internet for reviews, journal articles and clinical guidelines regarding recent advances in ultraviolet therapy for wound healing, no matter the level of evidence.

Outcomes

We performed a search in PubMed, and in the electronic resources offered by ANELIS of ANCS - UEFISCDI (The National Agency for Scientific Research and Innovation from Romania), as well as a free search on the Internet.

In the last 2 years, 1609 items containing the terms wound healing and ultraviolet have been published, most of them regarding the negative effects of ultraviolet healthy tissue exposure.

Searching PubMed Clinical Queries for the terms "ultraviolet" and "wound healing", we found 8 systematic reviews, 201 clinical studies and 48 studies of medical genetics.

The relevant reviews are the following:

a) Phototherapy for treating pressure ulcers. Chen C et al. Cochrane Database Syst Rev. 2014 (4). The review takes into consideration only RCT studies and its conclusion regarding ultraviolet applications is that there is not enough evidence to indicate a beneficial effect of ultraviolet exposure for wound healing, because the positive results of small studies must be cautiously interpreted.
b) Management of chronic pressure ulcers: an evidence-based analysis. Health Quality Ontario (2009) (5). The review considers that there is not enough evidence to indicate a beneficial effect of ultraviolet exposure for wound healing.

The same is stated by different guidelines and best practices regarding wound care from all around the world (6, 7, 8, 9).

The Clinical Practice Guideline concerning pressure ulcers developed by the American College of Physicians reports mixed result concerning light therapy on wound healing. They recommend light therapy for reducing ulcer surface areas (10).

The Wound Healing Society states that “Laser therapy and phototherapy have not been shown statistically to improve ulcer healing” (11).

The use of the magic word “statistics” here shows that there exist clinical evidences of lesser degree that

indicate the beneficial effect of UV exposure in wound healing.

We found in the NCBI the following orientation articles written by the team of Dr. M. Hamblin from Harvard, which take into account the results of evidences of level 4 and 5:

a) Hamblin MR et al. Ultraviolet Radiation in Wound Care: Sterilization and Stimulation. (2013) (12).
b) Yin R, Hamblin MR et al. Light based anti-infectives: ultraviolet C irradiation, photodynamic therapy, blue light, and beyond. (2013) (13).
c) Dai T, Hamblin MR et al. Ultraviolet C irradiation: an alternative antimicrobial approach to localized infections? (2012) (14).

These papers are reviewing the previous work regarding in vitro, in vivo on animal model experiments, and clinical studies, in which ultraviolet applications showed beneficial effects in wound healing.

We corroborated this information with expert opinions, expressed in books regarding wound care (15, 16).

a) Wound healing

Experiments on animal models (rats and rabbits) showed that UVA and UVB exposure induce a signifficantly higher rate of healing, when compared with non-exposed wounds. The tension is maintained at wound level, until day 15. El Batouty showed that UVA and UVB increase the speed of wound healing, the reepithelization rate and the collagen deposition, in wounds affecting all the layers of the skin. Pretreatment approach (UV exposure before wound was made) gave unconclusive results. Exposure to UVC, for 30 seconds a day, 5 days, induced changes in wound contraction, as result: a smooth passing from the repair tissue to the unharmed skin around the wound. constatarea lui Morykaw, anume ca expunerea la UVC a culturilor de fibroblaste determina o secretie sporita de fibronectina (15). UVC radiations produce less hypertrophic repair tissue in unexposed wounds on the same animal subject, indicating that UVC have systemic effects, too (17).

Clinical studies, reviewed by Hamblin and his team, are just a few and included a reduced number of subjects, but they generated beneficial results. The studies included subjects with pressure ulcers, diabetic ulcers, venous insufficiency low limb ulcers. We must take into account the fact that the trials include subjects with wounds unresponsive to standard treatment, mainly because of the underlying pathology, associated with old age. One randomized controlled trial on elderly subjects with pressure ulcers resulted in improved healing rates. Another study, on subjects with venous insufficiency, applied a combined approach: UV in E1 dose on the healthy skin around the wound and on the granulation tissue, and UV in E4 dose on the necrotic tissue in the lesion. One study, using UV exposure for 150 seconds, once a week, for 5 sessions, on chronic unresponsive ulcers, conducted in 1965, resulted in clean and healthy granulation tissue and in some cases, with complete healing (18).

Application of UVB for three times a week, for 6 weeks, on lower limbs pressure ulcers, resulted in reducing the quantity of exudate, reducing the depth of the ulcers, as well as an improvement of the aspect of the wounds (19).

UVC of 250 nm exposure, in E1 dose, for 15 seconds on the granulation tissue, and in E3 for 90 seconds, on the infected tissue of the wound, induced complete healing of an infected low limb diabetic ulcer (no recurrence at 3 month follow-up) (20). UVC of 254 nm, applied for 180 s, irradiance of 15.54 mW/cm^2) eradicated the MRSA infection and induced tendency for wound closure (healthy granulation tissue, epithelial buds and improved epithelization, return to normal skin color arround the wound (21). UVC exposure combined with ultrasound therapeutic application seem to be more efficient in wound healing than LASER therapy (21).

The combination of UVA, UVB and UVC has been applied in a randomized placebo controlled trial, reducing the time required by the healing process (6.3 weeks for the treated wounds, compared to 8.4 weeks for placebo treated wounds. The difference persisted unchanges when analysis of covariance was undertaken taking into account the age of the patients and the initial size of the wound (21).

It is difficult to compare these studies, because the wavelength of the UV radiation, the source of UV emission, the distance between the source and the treated wound, the treatment time, are different between them.

b) The antimicrobial applications of UV in wounds

Again, Hambin and his team summed the results of the studies up to 2013.

Animal models. A single exposure at UV of 254 nm for 2.59 J/cm^2 reduced signifficantly the microbial burden (10 fold) in mouse infected wounds. The treatment was beneficial in wounds infected with Pseudomonas aeruginosa and Staphylococcus aureus. The survival rate of the mice was improved (with 68% for Pseudomonas infected mice), and healing rate was

increased (with 31%, for Staphylococcus infected mice).

UVC exposure (254 nm) reduces fungal burden, in third degree burns, by 99% at 30 minutes after infection, and at 96% at 24 hours after infection (12).

Even if some mammalian cells were damaged, too, the damage was mainly repaired due to the UV exposure, too (22).

Clinical studies show the antimicrobial potential of UVC radiations in non-toxic doses for human tissues: UVC of 250 nm administered in a E3 dose on infected wound solved the infection and stimulated the healing of the wound. UVC of 254 nm, administered at a power density of 15.54 mW/cm^2 for 180 seconds induced reducing the MRSA bacterial burden of wounds and wound healing (12).

Using UV for antimicrobial puropose has some advantages: cost effectiveness (compared to chemical antibiotics), fast effect (less than 1 hour), due to topical application, UVC can eradicate resistant and pathogenic microorganisms much more rapidly than most antibiotics, lack of local and systemic chemical toxicity (13).

c) Dosing the UV application

Dose is important, generally, the effect of a therapeutical approach being directly proportional to the quantity of therapeutic agent administered, but the signaling role of the UV radiations may be more important than the actual amount of energy these photons bring to living tissue cells. It Is known that there is need of just a low-dose UVB exposure to induce the production of vitamin D in the skin (12). Biostimulation requires extremely low doses, occuring even at exposures of 0,001J/cm^2. But, there are doses exceeding the support capacity of the exposed tissue, and these doses are biosuppressive (23).

Suo et al., cited by Hamblin, investigated the effect of UVC (254 nm) on the expression of TGF-β on full-thickness dermal wounds in rats. Expression of growth factors was found higher after lower dose exposure than after 4 times increased exposure, at different moments in follow up (12).

Even if UV application are not used as a rule for wound healing, the experts in wound care recommend using ultraviolet phototherapy in chronic, infected and necrotic wounds. The suggested dose: 15 mW, for 30 seconds, applied as unique exposure, on the fresh washed wound (15).

Some authors think that judicious natural UV exposure might be beneficial for wound healing and for skin homeostasis broadly speaking. They propose that moderate UV exposure should be commenced early in the healing process of cutaneous wounds (24). The experts state the importance of education and awareness regarding wound care and the use of the different tools to manage it (25).

CONCLUSIONS

Even if the main part of the literature regards the damage induced by UV natural and artificial radiations, and the official evidence based guidelines regarding wound care avoid recommending UV exposure for wound healing, recently, the expert opinion is shifting toward the idea that controlled UV exposure might be beneficial for wound healing and skin homeostasis. In order to achieve benefits form UV exposure, one must take into account the sensible relationships between wavelength and penetration, time of exposure, energy emitted by the source and distance from the source to the exposed area, the degree of reflectance and absorption of UV in the skin and the damaged exposed tissues of the to be treated area, the minimal erythemal dose for the healthy skin, the underlying pathology and comorbidities, the medication, the nutritional and hydric status of the subject.

There are some issues to be managed in the future, in order to ensure safe use of UV in wound care. There is need for high-level evidences regarding UV effects in wound healing. New high-efficient light delivery technologies are needed, and optical clearing techniques, in order to provide a better penetration of UV and to reduce the side effects of UV treatment.

Conflicts of interests

None.

REFERENCES

1. International Classification of Functioning, Disability and Health (ICF). http://www.who.int/classifications/icf/en/
2. Vandersee S, Beyer M, Lademann J, Darvin ME. Blue-Violet Light Irradiation Dose Dependently Decreases Carotenoids in Human Skin, Which Indicates the Generation of Free Radicals. Hindawi Publishing Corporation, Oxidative Medicine and Cellular Longevity, Volume 2015, Article ID 579675, 7 pages, http://dx.doi.org/10.1155/2015/579675
3. Chang HY, Sneddon JB, Alizadeh AA, Sood R, West RB, Montgomery K, et al. Gene expression signature of fibroblast serum response predicts human cancer progression: similarities between tumors and wounds. PLoS Biol. 2004 Feb;2(2):E7. Epub 2004 Jan 13.
4. Chen C, Hou WH, Chan ES, Yeh ML, Lo HL. Phototherapy for treating pressure ulcers. Cochrane Database Syst Rev. 2014 Jul 11;7:CD009224. doi: 10.1002/14651858.CD009224.pub2.
5. Health Quality Ontario. Management of chronic pressure ulcers: an evidence-based analysis. Ont Health Technol Assess Ser. 2009;9(3):1-203. Epub 2009 Jul 1.
6. Nikitovic M, Brener S. Health Technologies for the Improvement of Chronic Disease Management, A Review of the Medical Advisory Secretariat Evidence-Based Analyses Between 2006 and 2011. Ont Health Technol Assess Ser. 2013;13(12):1–87.

7. European Pressure Ulcer Advisory Panel and National Pressure Ulcer Advisory Panel. Treatment of pressure ulcers: Quick Reference Guide. Washington DC: National Pressure Ulcer Advisory Panel; (2009).
8. National Institute for Health and Care Excellence. Pressure ulcers: prevention and management of pressure ulcers. NICE clinical guideline 179. 2014. available from: https://www.nice.org.uk/guidance/cg179
9. American Society of Plastic Surgeons. Evidence-based Clinical Practice Guideline: Chronic Wounds of the Lower Extremity. online at:http://www.plasticsurgery.org/
10. Qaseem A, Humphrey LL, Forciea MA, Starkey M, Denberg TD. Treatment of Pressure Ulcers: A Clinical Practice Guideline. From the American College of Physicians. Clinical Guidelines. Ann Intern Med. 2015;162(5): 370-379
11. Robson MC, Barbul A. Wound Healing Society. Guidelines for the best care of chronic wounds. Wound Repair Regen. 2006;14:647-710.
12. Gupta A, Avci P, Dai T, Huang YY, Hamblin MR. Ultraviolet Radiation in Wound Care: Sterilization and Stimulation. Adv Wound Care (New Rochelle). 2013 Oct; 2(8): 422–437
13. Yin R, Dai T, Avci P, Jorge AE, de Melo WC, Vecchio D, Huang YY, Gupta A, Hamblin MR. Light based anti-infectives: ultraviolet C irradiation, photodynamic therapy, blue light, and beyond. Curr Opin Pharmacol. 2013 Oct; 13(5):10.1016
14. Dai T, Vrahas MS, Murray CK, Hamblin MR. Ultraviolet C irradiation: an alternative antimicrobial approach to localized infections?. Expert Rev Anti Infect Ther. 2012 Feb; 10(2):185-195.
15. Conner-Kerr T, Albaugh K, Bell A, Phototherapeutic Applications for Wound Management, page 669-683, in Wound Care: A Collaborative Practice Manual for Health Professionals (Sussman C and Bates-Jensen B) Fourth ed. Ed. Lippincott, Williams and Wilkins; 2012.
16. Romanelli M ed. Science and Practice of Pressure Ulcer Management. London: Springer-Verlag; 2006.
17. Basford JR, Hallman HO, Sheffield CG, Mackey GL. Comparison of cold-quartz ultraviolet, low-energy laser, and occlusion in wound healing in a swine model. Arch Phys Med Rehabil. 1986;67:151
18. Freytes HA, Fernandez B, Fleming WC. Ultraviolet light in the treatment of indolent ulcers. South Med J, 1965; 58:223 -6.
19. Onigbinde AT. Adedoyin RA. Ojoawo OA. Johnson OE. Obembe AO. Olafimihan FK. Omiyale OM. Oniyangi S. Effects of ultraviolet radiation (type B) on wound exudates, appearance and depth description. Technol Health Care. 2010;18:297.
20. Chandrasekaran B, Chettri R, Agrawal N, Sathyamoorthy C, Short-term multimodal phototherapy approach in a diabetic ulcer patient. Singapore Med J2012;53:e122.
21. Thai TP, Keast DH, Campbell KE, Woodbury MG, Houghton PE, Effect of ultraviolet light C on bacterial colonization in chronic wounds. Ostomy Wound Manag 2005;51:32
22. Sevgi M Toklu A, Vecchio D, Hamblin MR. Topical Antimicrobials for Burn Infections – An Update. Recent Pat Antiinfect Drug Discov. 2013 Dec; 8(3): 161-197.
23. Jan Tuner, Lars Hodde. The Laser Therapy Handbook. Prima Books AB, 2004.
24. Rennekampff HO Busche MN, Knobloch K, Tenenhaus M. Is UV radiation beneficial in postburn wound healing? Medical Hypotheses. 2010;75(5): 436-8.
25. Werdin F, Tenenhaus M, Schaller HE, Rennekampff HO. Evidence-based Management Strategies for Treatment of Chronic Wounds. Eplasty. 2009; 9: e19.