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Review

The effect of phototherapy on neutrophils

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ABSTRACT

Background: The role of phototherapy on neutrophils has not been reviewed previously. This novel and non-invasive therapeutic approach is of particular interest for potential use in the treatment of pathologic processes in dermatology and infectious diseases in which neutrophils are the primary culprit.
Objectives: The primary aim of this study was to systematically review the role of phototherapy on neutrophils.
Method: Original publications were identified through searches in PubMed, Medline, Ovid, and the Cochrane Library. Search terms used included "phototherapy and neutrophils," "light therapy and neutrophils," and "laser and neutrophils." Studies were selected based on the level of evidence-based research.
Results: The literature search revealed a total of 22 controlled laboratory studies that evaluated the role of phototherapy on neutrophils. Among the effects of phototherapy noted were increases in: the respiratory burst of neutrophils, apoptosis of polymorphonuclear cells, and plasma NO and iNOS mRNA. Other notable findings include decreased: number of neutrophils in areas of inflammation, ROS production, neutrophil anti-apoptotic factors, and IL-1β concentration. Studies on PDT demonstrated neutrophilia and resultant decreased tumor growth.
Conclusion: Evidence indicates that phototherapy has a significant impact on neutrophils, the effect of which varies according to the specific type of phototherapy. These findings have a variety of potential clinical applications including the treatment of various autoimmune conditions, inflammatory diseases, and cancers.

Contents

1. Introduction

Phototherapy is well known to the field of dermatology, particularly for the treatment of psoriasis. It has been shown that its effects on psoriasis are due to keratinocyte modifications and selective depletion of intraepidermal T-cells [1]. One example is photodynamic therapy (PDT), which is a form of phototherapy that uses a photosensitizer, activated by light, to produce reactive oxygen intermediates that selectively destroy cells. PDT is currently used for the treatment of actinic keratosis, basal cell carcinoma, and Bowen's disease [2].

There is increasing evidence that phototherapy has the ability to modulate the immune system. These immunomodulatory effects are exemplified by ultraviolet (UVB) treatment of psoriasis in which UVB induces T cell depletion and release of immune mediators [3]. In addition to its immunomodulatory capabilities, phototherapy also has anti-bacterial properties which have previously been exploited for the disinfection of blood products and the treatment of various infections [4]. More recently, PDT has been studied for the treatment of oropharyngeal candidiasis [5], periodontitis [6], wound infections, and *Helicobacter pylori* infections [7]. The promising results of these

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studies further highlight the strong clinical potential for such a non-invasive and non-toxic therapeutic modality. It is of particular interest that phototherapy can be used in diseases that require chronic treatment or present as recalcitrant and opportunistic infections.

However, little has been reviewed with regard to other modes of action of phototherapy. The role of phototherapy on neutrophils is of particular interest for potential applications in the treatment of dermatologic conditions, autoimmune diseases, and infectious diseases in which neutrophils are the primary etiologic factor. These include peritonitis, pleurisy, gout, Crohn's disease, and rheumatoid arthritis as well as many others. Phototherapy could be the primary treatment modality or be used as an adjuvant to enhance resolution and recovery. The purpose of this manuscript is to evaluate potential applications of phototherapy with the intended goal of neutrophil modulation.

2. Methods

A search of published literature was performed using PubMed and the Cochrane Library. The search terms used to identify studies for inclusion in the review were "neutrophils" and "phototherapy," "laser," "pulsed dye laser," "blue light," "red light," and "tungsten." Other search terms used included "neutrophils" and "pleurisy," "gout," "rheumatoid arthritis," "Crohn's disease," "ulcerative colitis," "urinary tract infections," "appendicitis," "peritonitis," "airway disease," "neutrophilic dermatoses," "dapsone," "clofazimine," "cyclosporine," "doxycycline," or "hydroxychloroquine." Cited references from reference lists were also evaluated for possible inclusion. Included studies were restricted to articles written in the English language. Only controlled laboratory studies were included in the review. Case reports, non-controlled studies, and retrospective studies were excluded.

3. Results

The literature search revealed a total of 22 controlled laboratory studies that evaluated the role of phototherapy on neutrophils (Table 1). Of these studies, 4 utilized Helium–Neon (He–Ne) and Nitrogen low-level laser therapy (LLLT); 7 utilized Gallium–Aluminum–Arsenide (Ga–Al–As), Gallium–Arsenide (Ga–As), and Indium–Gallium–Aluminum–Phosphorus (In–Ga–Al–P) LLLT; and 11 utilized PDT.

3.1. He–Ne and Nitrogen LLLT

Four controlled laboratory studies were identified that evaluated the effects of He–Ne and nitrogen lasers on neutrophils (Table 2). In 1989, Karu et al. found that the He–Ne laser caused a 180–250% increase in both spontaneous and *Candida*-induced chemiluminescence of neutrophils and that the maximum effective dose of radiation was 0.02 J/cm^2 [8]. This was the first study to demonstrate that the He–Ne laser could induce the respiratory burst of neutrophils. In 2001, Duan et al. confirmed these results and investigated the signal transduction pathway involved in this He–Ne laser-induced respiratory burst of neutrophils. They found that the maximum effective dose of radiation to induce the respiratory burst was 0.03 J/cm^2. Further, they showed that protein tyrosine kinases (PTKs), protein kinase C (PKC), and phopholipase C (PLC) are required for the laser-induced respiratory burst of neutrophils [9]. In 2005, Hemvani et al. evaluated the effect of nitrogen and He–Ne lasers on percent apoptosis of human polymorphonuclear cells (PMNs), including neutrophils, in normal versus burn patients. They found that the nitrogen laser significantly increased percent apoptosis in normal ($p<0.03$) and burn patients ($p<0.008$) exposed for 5 or 10 min. The He–Ne laser increased apoptosis only in normal patients exposed for 10 min ($p=0.005$) [10]. In 2007, Abdel et al. investigated the effect of the He–Ne laser on plasma nitric oxide (NO) and inducible nitric oxide synthase (iNOS) in neutrophils from healthy patients versus Duchenne muscular dystrophy (DMD) patients. They found that the He–Ne laser increased plasma NO by 207% in normal ($p<0.000001$) and 183% in DMD patients ($p<0.000001$). Levels of iNOS mRNA were increased by 48% in normal ($p<0.0000001$) and 142% in DMD patients after irradiation ($p<0.00001$). The He–Ne laser also caused a reduction in markers of oxidative stress in the DMD patients [11]. This study demonstrated

Table 1
Laser characteristics and radiation dosage in included studies

Study, year	Laser type	Mean output power (mW)	Power density (mW/cm^2)	Radiation dose (J/cm^2)
Karu et al., 1989 [5]	He–Ne, 632.8 nm	Not given	0.68	0.01–0.03
Krosl et al., 1995 [16]	Photofrin-based PDT, 630 nm	35	45	60
de Vree et al., 1996 [17]	Photofrin-based PDT, 625 nm	Not given	Less than 50 mW/cm	270 J/cm
de Vree et al., 1997 [18]	Photofrin-based PDT, 625 nm	Not given	Less than 50 mW/cm	270 J/cm
Duan et al., 2001 [6]	He–Ne, 632.8 nm	Not given	Not given	0.005–0.1
Cecic et al., 2001 [19]	Photofrin-based PDT, 630 nm; tetra(*m*-hydroxyphenyl)-chlorine (mTHPC)-based PDT, 652 nm	1,000,000	100–120	Photofrin-based PDT: 60–150; mTHPC-based PDT: 100
Cecic et al., 2002 [20]	Photofrin-based PDT, 630 nm	150,000	110–120	60
Sun et al., 2002 [21]	Photofrin-based PDT, 630 nm; mTHPC-based PDT, 652 nm	Photofrin-based PDT: 150 W; mTHPC-based PDT: 0.25 W	Photofrin-based PDT: 110–120; mTHPC-based PDT: 120–130	Not given
Gollnick et al., 2003 [22]	2-[1-hexyloxyethyl]-2-devinyl pyropheophorbide-a (HPPH)-based PDT, 665 nm	75	75	100–135
Fujimaki et al., 2003 [9]	Ga–Al–As, 830 nm	1000	150	9.5 and 19.0
Kobayashi et al., 2004 [23]	Mono-L-aspartyl chlorine 6-based-PDT, 664 nm	Not given	Not given	10
Aimbire et al., 2005 [10]	Ga–Al–As, 685 nm	12	150	2.5
Lopes–Martins et al., 2005 [11]	In–Ga–Al–P, 650 nm	2.5	31.25	3, 7.5, and 15
Hemvani et al., 2005 [7]	Nitrogen, 337 nm; He–Ne, 632.8 nm	3	Not given	Not given
Cecic et al., 2006 [24]	Photofrin-based PDT, 630 nm	150,000	100	150
Cecic et al., 2006 [25]	Photofrin-based PDT, 630 nm	150,000	100	150
Correa et al., 2007 [12]	Ga–As, 904 nm	4	50	3, 7.5, and 15
Abdel et al., 2007 [8]	He–Ne, 632.8 nm	10	Not given	2.5
Kousis et al., 2007 [26]	HPPH-based PDT, 665 nm	Not given	7 and 14	48 and 128
Aimbire et al., 2008 [13]	Ga–Al–As, 660 nm	30	38.22	7.5
Barbosa et al., 2008 [14]	Ga–As, 685 nm	29	145	4.2
Aimbire et al., 2008 [15]	Ga–Al–As, 660 nm	30	38.22	7.5