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Photodynamic Therapy as an Effective and Safe Treatment for pediatric Cutaneous Diseases: A Systematic Review

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Abstract

Background: Although the application of Photo-Dynamic Therapy (PDT) has been increased for the treatment of cutaneous disease in adults with various skin problems, it seems that the effectiveness of the approach has been less investigated in children. Therefore, this systematic review aimed to assess the application of photodynamic therapy in children with skin disease.

Methods: The present review has followed Cochrane's methods for conducting systematic reviews of interventions. Relevant studies were collected by searching four electronic databases, including PubMed, Scopus, Medline, and Web of Sciences using such keywords as "photodynamic therapy " and "PDT", in combination with "cutaneous disease ", "skin disease ", and "Children" or "pediatric" up to 2022.

Results: In total, 42 studies were included in this review, among which 14 were conducted on patients with acne vulgaris (treatment success rate: 26.3% to 100%) and eight articles studied plantar warts and condyloma acuminatum (treatment success rate: 30% to 100%). Other cutaneous diseases in children treated by PDT included porokeratosis, port-wine stain, basal cell carcinomas, leishmaniasis, tinea capitis, xeroderma pigmentosum, Langerhans cell histiocytosis, lymphomatoid papulosis, and Bowen's disease, with treatment success rates between 30% and 100%.

Conclusion: It seems that PDT has a treatment potential to be used for children with cutaneous disease. However, due to the existence of non-uniform parameters for PDT treatment, optimization of the treatment protocol (distinct for each disease) is necessary to ensure a better result with long-term remission in children with cutaneous disease.

Key Words: Aminolevulinic acid, Cutaneous disease, Photodynamic therapy, Photosensitizer.

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1- INTRODUCTION

At the beginning of the twentieth century, Photo-Dynamic Therapy (PDT) was introduced as a treatment approach for cutaneous diseases such as actinic keratosis, in situ Squamous Cell Carcinoma (SCC), and superficial and nodular basal cell carcinoma (BCC) (1-4). However, the Food and Drug Administration (FDA) confirmed the application of this approach only for facial non-hyperkeratotic actinic keratosis (4, 5). Some evidence suggested the application of PDT in acne vulgaris, rosacea, sebaceous hyperplasia, warts, and leishmaniasis (2, 5). The main advantage of PDT is that it acts selectively. In other words, it can destroy the diseased cells, while having no effect on normal surrounding tissues. Moreover, the phenomena can be repeated, unlike radiation therapy (6). In PDT, a photosensitizing agent, which can be delivered systemically (e.g., porfimer sodium) or topically (e.gd-5-aminolevulinic acid (ALA) or methyl aminolevulinate) in combination with light is used to cause selective damage to the target tissue (6). Various light sources such as blue light, red light, intense pulsed light (IPL), and the pulsed-dye laser can be used in PDT based on different factors including the type of photosensitizer and medical conditions. Burning and pain during light exposure are the most common side effects of PDT, which can limit the use of this approach in children (7). However, the literature shows a rising trend in the use of PDT for the treatment of children with cutaneous disease. Several systemic studies assessed the effects of PDT in the treatment of cutaneous diseases in adults with various skin problems (1, 8-10). However, it seems that the effectiveness of the approach has been investigated less in children (7). This systematic review aimed to assess the effectiveness of photodynamic therapy in children with cutaneous disease.

2- MATERIALS AND METHODS

This systematic review was conducted on studies assessing the effects of PDT on children with cutaneous disease. The structure of this study followed Cochrane's methods for conducting systematic reviews of interventions in seven steps including asking a question, specifying the eligibility criteria, searching databases, removing the irrelevant articles based on the eligibility criteria, assessing the quality assessment, extracting important data, and evaluating and discussing the obtained data (11).

2-1. Inclusion and exclusion criteria

In the present study, PICO criteria (Participants, Intervention, Comparison, and Outcome) were applied for the inclusion of the studies. Inclusion criteria were 1) examination of human samples, 2) provision of a clear description of the application of the methodological technique in the treatment of PDT in patients with cutaneous disease, 3) age <18 years, and 4) publication in English. Exclusion criteria were 1) studies on the application of PDT in the treatment of diseases other than a cutaneous disease, 2) studies with insufficient data, 3) studies conducted on patients older than 18, 4) in vitro studies, 5) animal studies, 6) non-interventional and non-therapeutic studies, 7) narratives, reviews, and systematic/meta-analyses, 7) editorial letters or consensus statements in which no patient was treated by PDT, and 8) qualitative studies. All case reports, case series, retrospective and prospective articles, comparative case controls, as well as randomized clinical trials were included in this review.

2-2. Literature search

In the present systematic review, four electronic databases, including PubMed,

Scopus, Medline, and Web of Sciences, were searched up to 2022. It should be noted that we also performed a manual search using other databases such as Google and Google Scholar to find relevant studies and published reviews on the effects of PDT on cutaneous disease. The search process was carried out using such keywords as "photodynamic therapy" and "PDT", in combination with "cutaneous disease", "skin disease", and "Children" or "pediatric". Search strategies were applied by two trained researchers based on the predetermined goals.

2-3. Study design and data extraction

In the first step, all the articles on the effects of PDT on children with cutaneous disease published up to 20 February 2022 were searched using the aforementioned keywords. Two trained researchers searched PubMed, Scopus, Medline, and Web of Sciences databases independently for relevant articles from 15 July to 15 August 2022. Moreover, other databases such as Google and Google Scholar were searched for future relevant studies. We also reviewed the reviews found on the effects of PDT on cutaneous diseases to make sure that we did not miss any relevant studies in our search. Researchers reviewed the titles and abstracts of articles together and removed irrelevant studies based on the eligibility criteria. In cases where we could not determine the eligibility of the study by viewing the study title and abstract, the full text of the article was extracted for further scrutiny. In the final stage of the selection or exclusion of studies, full-text versions of all the selected studies were extracted for more detailed evaluations. We included all retrospective or prospective studies adopting PDT as a therapeutic intervention. In cases where the study was not available, we tried to get the necessary information by sending an email to the corresponding author. **Fig. 1** presents the PRISMA flow diagram of the selection process of the included studies. Eventually, the necessary information was extracted from the selected studies with an eye to the objectives of the study.

The two researchers were continuously in contact with each other in order to exchange information and recorded the main data in a researcher-made form. The extracted information included sample size, type of cutaneous disease, age, male-to-female ratio, type of applied photosensitizer, irradiance dosage, number of treatment sessions, and percentage of success, side effects, and recurrences.

2-4. Quality Assessment

The quality of the entered articles (i.e., retrospective and prospective articles, comparative case-controls, and randomized clinical trials) was assessed using Cochrane criteria (12). The quality assessment of the selected articles was reviewed in terms of seven bias domains: sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other sources of bias (13). Based on the aforementioned criteria, low, high, and unknown risks of bias were recorded in a table by "Yes", "No", and "Unclear", respectively.

3- RESULTS

In total 2,323 papers were extracted in the first search of databases, of which 2,083 papers were excluded due to irrelevance or lack of focus on PDT in the treatment of cutaneous disease. Out of the 240 remaining studies, 107 duplicate papers were removed. In the next step, the studies with inaccessible full-text versions (n=2) and those published in languages other than English (n=3), editorial letters (n=5), books (n=9), qualitative and narrative review articles (n=53), systematic reviews (n=3), in vitro studies (n=7), animal studies (n=6), and educational series (n=2) were excluded from the present study. Moreover, another

study (n=1) assessing the prognostic value of PDT for preventing cutaneous disease was removed due to the lack of focus on the treatment value of PDT. Finally, 42 articles were selected and included in the review process (**Fig. 1**). All papers investigating the treatment value of PDT for the cutaneous disease were entered in this study.

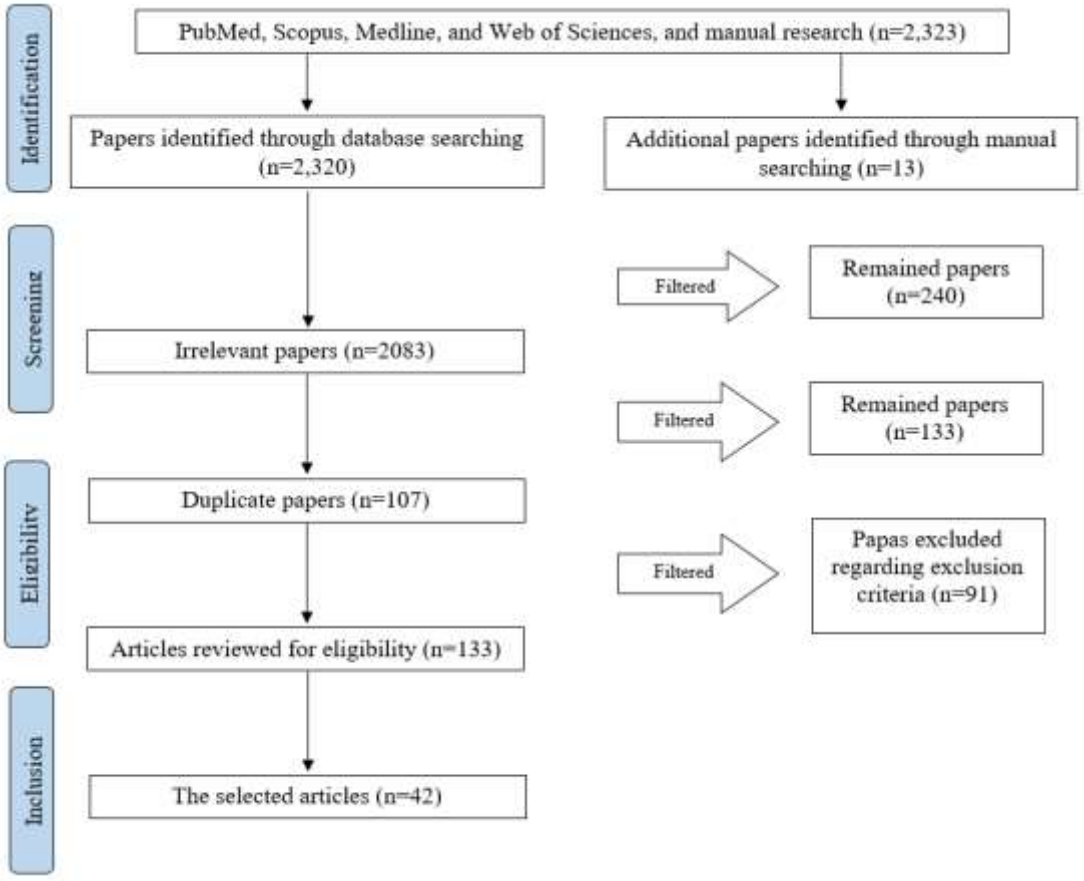

Fig. 1: PRISMA flowchart representing the study selection process

In total, 30.9% of articles were performed in European countries, including the UK (n=4), Spain (n=3) Sweden (n=2), France (n=1), Netherlands (n=1), Italy (n=1), and Slovak Republic (n=1). Moreover, 14 studies were conducted in the Far East, including China (n=12), Japan (n=1), Korea (n=1); and two studies were performed in south Asia (Taiwan and Thailand). A total of six (14.2%) studies were conducted in North America, including the USA (n=5) and Canada (n=1), one in South America (Chile), and three in Africa (Egypt). The data extracted from each article (type of cutaneous disease, sample size, number of patients aged <18 years, age, male to female ratio, type of photosensitizer, irradiation source, irradiance dosage, irradiation duration, number of treatment sessions, percentage of success, side effects, and recurrences) were evaluated in this review (**Table 1**).

From among 42 entered studies, 14 (33%) were conducted on patients with acne vulgaris, three of which were double-blinded, randomized, and placebo-controlled multicenter studies, two were case series, and eleven were comparative interventional studies.

Table-1: Information extracted from the reviewed studies

Author (years) Reference	Country	Type of study	Type of cutaneous disease	Sample Size (Groups)	Number of patients < 18 years	Age (year) (For children)	Male Female ratio (For children)	Photosensitiser	Irradiation sources	Irradiance (mW/cm^2)	Daily irradiation	Number of Treatment sessions	Percentage of success	Side effects	Recurrences
Papageorgiou et al. (2000) (24)	UK	Comparative interventional	Mild to moderate Acne vulgaris	107 Blue light: 30 mixed blue and red light: 27 cool White light: 25 Benzoyl peroxide cream: 25	No specified	14-50	73/34 No specified for children	--	Fluorescent lamps 4 ×15 W	Blue light at peak of 415 nm Mixed blue and red light at peaks of 415 and 660 nm	15 min	Four sessions every 4 weeks	76%	No side effects	No recurrence during 12 weeks
Tzung et al. (2004) (25)	Taiwan	Single blinded Comparative interventional	Facial acne vulgaris	28 PDT[1]:14 Control:14	No specified	15-32	10-18 No specified for children	--	Fluorescence under Wood's light	Blue light at peak wavelength of 420 nm (F-36 W/m with a irradiation of 40 J/cm^2)	--	Eight sessions twice weekly	52%	No side effects	No recurrence during 1 months
Pollock et al. (2004) (14)	UK	Case series	Moderate Acne vulgaris in the back	10	1	16-40 (16)	8/1 One female	ALA[2] 20% for 3 h	Fluorescent lamps	Red light at 635 nm, 25 mW cm^{-2}, 15 J cm^{-2}	10 min	Three sessions weekly	100%	Not reported	No recurrence during 3 weeks
Schroeter et al. (2005) (19)	Netherlands	Randomized interventional study	Plantar Warts	31 (48 lesions)	No specified	6-74	13/18 No specified for children	ALA 20% for 4-8 h	Incoherent multiple-band light source	Red light 580–720 nm	15-20 min	1-7 session with 2 to 4 weeks interval	88%	Hypopigmentation	No recurrence during 15 months
Oseroff et al. (2005) (26)	USA	Case report	BCC[3] and BFHs[4]	3	3	6-17	1/2 Systemic and topical PDT	ALA 2.5% to 20% (wt/wt)	Tungsten-halogen lamp	Red light at 33 to 100 J/ cm^2 at 40 to 100 mW/ cm^2 (laser) and 60 to 200 J/ cm^2 at 50 to 100 mW/cm2 (lamp)	20 to 50 min	4-7 sessions	100% (85% to 98% overall clearance)	Selective phototoxicity with rapid healing	Recurrence in one case and it was no reported in others during 3.2 years
Morton et al. (2005) (27)	UK	Comparative interventional study	Mild to moderate facial Acne vulgaris	30 10 m:14 20m:16	No specified	16–52	No specified for children	--	LED[5] prototype	Blue light at peak wavelength of 409–419 nm with dose of 48 J/ cm2 and intensity of 40	10-20 min	Eight sessions with a 3–4 days interval between for 4 weeks	76% at 8 weeks and 71 at 12 weeks	Slight redness (53%), dryness of skin (13%), and mild pruritus (16%)	No recurrence during 6 months

Author (years) Reference	Country	Type of study	Type of cutaneous disease	Sample Size (Groups)	Number of patients < 18 years	Age (year) (For children)	Male Female ratio (For children)	Photosensitiser	Irradiation sources	Irradiance (mW/cm^2)	Daily irradiation	Number of Treatment sessions	Percentage of success	Side effects	Recurrences
										Mw/cm2					
Rojanamatin et al. (2006) (28)	Thailand	Comparative interventional study (Pilot)	Facial acne vulgaris	14 Left side: IPL[6] Right side: ALA-IPL	No specified	16-27	No specified for children	ALA 20% for 30 minutes	Flashlamp-pumped IPL	Red light at peak wavelength 560-590 nm with total fluence between 25 and 30 J/cm2	2.4 and 6 milliseconds	Three sessions at 3- to 4-week intervals	66.8% - 87.7% at 12 weeks	Mild edema and minimal crust	No recurrence during 3 months
Hörfelt et al. (2006) (29)	Sweden	Double blinded, randomized, placebo-controlled multicentre study	Moderate to severe facial acne vulgaris	30 Left side: MAL[7]-PDT Right side: PDT alone	No specified	15-28	25/5 No specified for children	MAL (160 mg) for 3 h	Aktilite CL 128 lamp	Red light at wavelength 635 nm and light dose 37 J cm^{-2}	--	Two sessions every two 2 weeks	A greater reduction in the total inflammatory lesion in MAL-PDT than PDT group (54% vs. 20%)	Pain	No recurrence during 10 weeks
Asilian et al. (2006) (30)	Iran	Non blinded Randomized comparative clinical trial	Leishmaniasis	60 PDT 5% paromomycin And soft white paraffin-based ointment	No specified	>5	No specified for children	ALA 5% for 4 h	Wood's light	Red light 633 nm at 100 J/ cm2	--	Every week for 4 weeks.	93.5% More observed in ALA-PDT group	Mild pruritus, burning, redness, discharge, oedema and pain	No recurrence during 3 months
Hörfelt et al. (2007) (31)	Sweden	Non comparative interventional study (Pilot)	Mild to severe acne vulgaris in the back	15 light dose of 30 and 50 J/cm:10 light dose of 50 and 70 J/cm: 5	3	16-44	9/6 No specified for children	ALA 20% for 3 h	Waldman PDT 1200 lamp	Red light at 635 nm, light dose 30-70 J cm^{-2}	--	--	60%	Hyperpigmentation and pain	No recurrence during 10 weeks
Mao et al. (2008) (23)	China	Case report	FFWs[8]	3	1	15	Female	ALA 20% for 3 h	LED	Red light at wavelengths of 633 ± 6 nm and fluences of 126 J/cm2	--	Four sessions every week	100% after 4 weeks	Transient itching and burning	No recurrence
Loncaster et al (2009) (32)	UK	Non comparative interventional study	Gorlin syndrome developed	33 (138 lesions)	No specified	9-79	15/18 No specified for children	MAL cream (160 mg/g) or ALA	LED	Red light ate 100-200 J/cm2 (630±15 nm)	--	Two or more treatments during 4 weeks apart	56.3%	No side effects	No recurrence during 24 months.

Author (years) Reference	Country	Type of study	Type of cutaneous disease	Sample Size (Groups)	Number of patients < 18 years	Age (year) (For children)	Male Female ratio (For children)	Photosensitiser	Irradiation sources	Irradiance (mW/cm^2)	Daily irradiation	Number of Treatment sessions	Percentage of success	Side effects	Recurrences
			Multiple BCCs					20%							
Gracia-Cazaña et al. (2009) (33)	Spain	Case report	Linear Porokeratosis	1	1	13	Male	MAL hydrochloride in a 160 mg/g concentration for 3 hours	Aktilite lamp	Red Light at dose of 37 J/cm2	9 min	Two sessions one month apart	100%	Mild burning	No recurrence during 11 months
Barolet et al. (2010) (34)	Canada	Randomized, controlled, blinded trial	Mild to moderate acne vulgaris in the face and back	10 With and without pretreatment with IR[9]	No specified	13-54	No specified for children	20% ALA for 60 minutes	LED	Pretreatment: at 970nm (80mW/cm2, 72 J/cm2 up to 40 min Treatment: at 630nm (50mW/cm2, 70 J/cmy) for 23 min	15 min	One session	IR-PDT:73% PDT:38% P<0.005	Transient swellings and erythema	No recurrence during 12 months.
Chen et al. (2010) (22)	China	Case report	Condyloma acuminatum	1	1	9	Female	20% ALA for 3 h	He-Ne laser light	Wavelength of 630 nm	--	--	100%	Slight pain and mild labium minor edema for 1 day after PDT	No recurrence during 6 months.
Failla et al. (2010) (35)	Belgium	Case report	Langerhans cell histiocytosis	1	1	18 months	Male	MAL for three hours	LED	Red light red light at wavelength of 634 nm, 74 J/cm2	8 min	One session	100% after 4 weeks	No side effects	No recurrence after 6 months
Larson et al. (2012) (36)	USA	Case report	XPC[10]	1	1	16	Female	20% ALA for 40 minutes	--	Blue light wavelength of 417 to 432 nm	16 min	Three sessions	100%	No side effects	No recurrence
Pinto et al. (2013) (37)	Chile	Comparative interventional study	Facial acne vulgaris	36 (Red light alone and MAL-PDT)	No specified	>15	No specified	MAL (160 mg g) for 90 min	Waldman ® PDT 1200 lamp	Red light at wavelength of 635 nm, light dose 37 J/cm 2 and a fluence rate of 70 mW/cm 2)	9 min	Two sessions, 2 weeks apart	82.3% after two weeks	Pain, erythema and epithelial exfoliation	No recurrence during 10 weeks
Girard et al.	France	Case series	Multiple NBCCS[1]	7	2	7 and 17	Female	MAL for 3 h	LED lamp	Red light at wavelength of	10 min	Two treatments 7–	75% during 3	Intense discomfort	No recurrence

Author (years) Reference	Country	Type of study	Type of cutaneous disease	Sample Size (Groups)	Number of patients < 18 years	Age (year) (For children)	Male Female ratio (For children)	Photosensitiser	Irradiation sources	Irradiance (mW/cm^2)	Daily irradiation	Number of Treatment sessions	Percentage of success	Side effects	Recurrences
(2013) (38)			[1]							635 nm, 25 mW cm^{-2}		14 days apart	months	and pain in one case	during 4 and 13 months
Curkova et al. (2014) (39)	Slovak Republic	Case report	Linear porokeratosis	1	1	16	Female	MAL hydrochloride for 3 h	--	Dose of 37 J/cm2	--	Four during one month apart	100%	Burning during illumination	No recurrence during, I year
Asayama-Kosaka et al. (2014) (14)	Japan	Case series	Facial acne vulgaris	11	1	14-38	4/7 One male	5% ALA for 2 h	Broadband light system	At peak of 612 nm and 674 nm and ight delivery at a fluence of 15 J/cm2	--	One session	26.3%	Minimal to milde reported in 10 of 11 cases	Recurrence at four to 12 months in four patients
Gracia-Cazaña et al. (2015) (40)	Spain	Case report	Porokeratosis (Wiskott–Aldrich syndrome)	1	1	12	Male	MAL	--	Dose of 37 J/cm2	--	Three sessions	100%	Moderate pain	No recurrence during 5 years
Garrido-Colmenero et al. (2015) (41)	Spain	Case report	Porokeratoses	1	1	11	Female	MAL hydrochloride in a 160 mg/g concentration for 2 hours	Aktilite lamp	At dose of 37 J/cm2 for 8 minutes		Two sessions 3 weeks apart	100%	No reported	No recurrence during 11 months
Ma et al. (2015) (15)	China	Non comparative interventional study	Facial acne vulgaris	21	21	12-18	15/6 Systemic PDT	5% ALA for 60 min	Narrow band light-emitting diode	Red light at 75–80 mW/cm^2 and a light dose of 90–96 J/ cm^2	--	Three sessions	85.71%-95.23%	Transient and mild to moderate	No recurrence during 8 weeks
Tao et al. (2015) (42)	China	Non comparative interventional study	Facial acne vulgaris	136	The majority of patients were <18	18-38	92/44 No specified for children	3.6 % ALA	LED light	Red light at peak wavelength of 66 mw/cm2 for 20 min dose level of 126 J/ cm^2	20 min	Three sessions with an interval of 2 weeks	92.65%	Mild and transient	Papules and comedos at 8 weeks (mild relapse)
Tao et al. (2016) (43)	China	Non comparative interventional study	Facial acne vulgaris	125	No specified	14-35	38/87 No specified for children	3.6 % ALA for 1.5 h	LED light	Red light at peak wavelength of 66 mW/cm2 and a light dose	20 min	Three or four sessions	88.8% at 12 weeks	Mild and transient	Papules and comedos at 8 weeks (mild relapse)

Author (years) Reference	Country	Type of study	Type of cutaneous disease	Sample Size (Groups)	Number of patients < 18 years	Age (year) (For children)	Male Female ratio (For children)	Photosensitiser	Irradiation sources	Irradiance (mW/cm^2)	Daily irradiation	Number of Treatment sessions	Percentage of success	Side effects	Recurrences
										of 126 J/cm2.					
Hyun et al. (2016) (44)	Korea	Case report	Bowen's disease	1	1	12	Male	MAL for 3 hours	--	Red light	--	Two sessions at an interval of 3 weeks	100%	No side effects	No recurrence during 9 months
Pariser et al. (2016) (45)	USA	Double-blind, randomized vehicle-controlled study	Severe facial acne vulgaris	153 Case MAL:100 pelacebo: 53	94 cases	12-35	56/44	8% MAL for 1.5 h	LED light	Red light at peak wavelength of 635-nm red light, total dose 37 J cm-2	9 min 15 s	Four sessions 2 weeks apart	Better response to the treatment in case group than control group (44% vs. 26%)	Mild and transient	No recurrence during 12 weeks
Zhang et al. (2017) (46)	China	Case report	PWS[12]	2	2	1.5-3	1/1	HMME [13] (at a dose of 5 mg/ Kg)	LED green-light	Dosage of 535-nm	20 min	2-3 sessions	100%	No side effects	No recurrence during
Li-Qiang et al. (2018) (47)	China	Interventional study	PWS	82	82	1-14	33/49	HMME	LED green-light	Dosage of 532 nm with density between 80–85 mW/cm2	20–25 min	One session	70.7%	Pain and post-treatment edema	
Borgia et al. (2019) (21)	Italy	Case report	FFWs	1	1	8	Female	ALA for 30 min	Daylight	Daylight photodynamic therapy	2 h	Two sessions at 2 months interval	100% after 6 weeks	Mild burning	No recurrence during 12 months
Ahmed Abdul Latif et al. (2022) (16)	Egypt	Comparative study	Plane Warts (FFWs)	40 MB-PDT[14]:20 and TPPD[15]:20	40	5-13	11/29	Methylene blue hydrogel concentration was 0.1 %	Daylight	Daylight photodynamic therapy	--	Six sessions	A higher complete response reported in TPDD than MB-PDT (60% vs. 30%)	No side effects	No recurrence during 3 months
We et al. (2020) (48)	China	Case report	Tinea capitis	1	1	2	Male	20% ALA was	Diode Laser	At peaks of 635 nm diode laser of 100 J/cm2		Two sessions	100% after 1 months	Slight pain	No recurrence during 12

Author (years) Reference	Country	Type of study	Type of cutaneous disease	Sample Size (Groups)	Number of patients < 18 years	Age (year) (For children)	Male Female ratio (For children)	Photosensitiser	Irradiation sources	Irradiance (mW/cm^2)	Daily irradiation	Number of Treatment sessions	Percentage of success	Side effects	Recurrences
								applied for 3 h		and for 20 min					months
Nassar et al. (2020) (17)	Egypt	Controlled clinical trial	Plane warts	39 (Groups: IPL, immunotherapy, and control)	No specified	5-28	No specified for children	Methylene blue 10% solution for 60 min	IPL (hair mode)	At peaks of 610 and 660 nm, IPL, a fluence of 13–16 J/cm2	--	Three treatments at 2-week intervals	46.1%	Transient and mild of pain	No recurrence during 3 months
Khalaf et al. (2020) (49)	China	Interventional study	PWS	45	No specified	6-37	No specified for children	5 mg/kg HMME within 20 minutes	LED green-light	Dosage of 532 nm LED light and irradiation energy density between 80 and 110 J/cm2	15 min	Three sessions	97.78% More effective for children <18	Hyperpigmentation	No recurrence
Borgia et al. (2020) (18)	Italy	Randomized comparative study	FFWs	30 DL-PDT[16]: 15 C-PDT[17]: 15	30	< 18	7/8	10% ALA for 3 h	Daylight and LED	Daylight photodynamic therapy versus red light 160 mW/cm2 (Total light dose of 75 J/cm^2)	DL-PDT: 30 min 15 C-PDT: 8 min	Three times with 1-month intervals (Week 24)	Week 12 DL-PDT:53% C-PDT: 0% Week 24 DL-PDT: 73.3%% C-PDT: 80%	Transient pain, irritation and hyperpigmentation	No recurrence
Snider et al. (2020) (50)	USA	Case report	Lymphomatoid papulosis	1	1	13	Male	20% ALA for 1 h	LED	Dose of 10 J/cm^2	--	Three times every 2 weeks	100% after two months	Pain during irritation	Recurrence 2 years later
Author (years) Reference	Country	Type of study	Type of cutaneous disease	Sample Size (Groups)	Number of patients < 18 years	Age (year) (for children)	Male Female ratio (for children)	Photosensitiser	Irradiation sources	Irradiance (mW/cm^2)	Daily irradiation	Number of Treatment sessions	Percentage of success	Side effects	Recurrences
Chun et al (2021) (51)	China	Non comparative interventional study	PWS	439	439	--	--	Hemoporfin	LED	532-nm green light for 20-25 min	--	Two times	95.2%	Transient swelling, purpura, crusts, and pigmentation	No recurrence
Zhang et al. (2022) (52)	China	Non comparative interventional study	PWS	107	107	--	--	Hemoporfin	LED	532 nm green light for 20 min with a power density of 80-100 mW/cm2	Eight weeks	Two times	96.9%	No side effects	No recurrence

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Yin et al. (2022) (20)	China	Case report	Condyloma acuminatum	1	1	2	Male	ALA	--	--	--	Five rounds with a treatment interval of 7 days	100%	No side effects	No recurrence during 6 months
Knapp et al. (2022) (53)	USA	Case report	Leishmaniasis	1	1	13	Male	ALA	--	--	--	--	100%	No side effects	No recurrence during 6 months
Abdullah et al. (2022) (54)	Egypt	Randomized controlled comparative clinical study	Tinea capitis	52 (four groups of 13)	13	<18	--	Curcumin loaded in nanospanlastics	--	--		--	46%	Mild tolerable burning pain	No recurrence 6 months

1-Photodynamic Therapy, 2- d-5-Aminolevulinic Acid, 3-Basal Cell Carcinomas, 4-Basaloid Follicular Hamartomas, 5-Light-Emitting Diode, 6-Intense Pulsed Light, 7- Methyl Aminolevulinate, 8- Facial Flat Warts, 9-Radiant Infrared, 10-Xeroderma pigmentosum type C, 11-Nevoid Basal Cell Carcinoma Syndrome, 12-Port-Wine Stains, 13- Hematoporphyrin Monomethyl Ether, 14-Methylene Blue Day Light Photodynamic Therapy, 15-Tuberculin Purified Protein Derivative, 16- Daylight Photodynamic Therapy, 17-Conventional Photodynamic Therapy

The samples comprised 1,167 patients treated with PDT. Irradiance sources were blue light (at peak wavelength between 409 and 420 nm with irradiation of 40 J/cm2 for 10-20 min) in four studies and red light in nine studies (at peak wavelength between 415 and 660 nm with irradiation of 25-126 J/cm2 for 10-20 min). The treatment sessions ranged between one and eight. The final mean improvement was in the range of 26.3% and 100% for the treatment of acne vulgaris using PDT. Side effects such as pain, edema, and dryness of skin, pruritus, epithelial exfoliation, and hyperpigmentation were transient and mild to moderate in all studies. Recurrence was reported in one study (14). Only one study has been focused on patients under 18 years of age (15). Since the number of children entered in the aforementioned studies was not specified, we could not estimate the exact treatment success rate of PDT applied on children with acne vulgaris.

Among the entered studies, seven had assessed the effect of PDT on the treatment of children with plane warts caused by Human Papilloma Viruses (HPV), Including Facial Flat Warts (FFW) (n=5), condyloma acuminatum (n=2), and plantar wart (n=1). It is worth mentioning that three of these studies were comparative clinical trials (16-19) and the others were case reports (20-23). The number of patients treated with PDT due to warts caused by HPV was 100 cases. Irradiance sources were red light in nine studies (at peak wavelength between 100 and 660 nm with irradiation of 75-126 J/cm2 for 10-20 min) and daylight photodynamic therapy for 30 min to 2 hours. The number of treatment sessions was between two to six sessions. ALA 10%-20% and methylene blue (10%) have been used as photosensitizers. The final mean improvement rate of PDT on the treatment of lane wart caused by HPV ranged from 30% to 100%. Side effects included transient itching, burning, slight pain, mild labium, edema, and hyperpigmentation, which were mild in all studies, and no recurrence was reported in any study. Moreover, five studies were focused on children, and three were conducted on both children and adults.

In total, four studies assessed the effect of PDT on the treatment of children with porokeratosis, all of which were case reports. The age range was 11-16 years and the female/ male ratio was 1:1. In all of these studies, irradiation dosage of 37 J/cm2 for 8 to 9 min and MAL hydrochloride at a concentration of 160 mg/g was used as a photosensitizer for 2 or 3 h. The number of treatment sessions was between two to four. The final improvement using PDT in the treatment of porokeratosis was 100%. Side effects included transient mild to moderate burning and pain with no recurrence.

Three studies assessed the effect of PDT in the treatment of port-wine stain (PWS), four clinical studies, and one case report on 675 cases (both adults and children); and in all of these studies, 532 nm LED green light was irradiated with a density of 80-85 mW/cm^2 for 15-25 min and HMME at 5 mg/kg, used as a photosensitizer. The number of treatment sessions was between one and three. Final PDT improvement for PWS treatment ranged from 70% to 100%. Side effects included transient edema, pain, and hyperpigmentation with no recurrence.

The effect of PDT on the treatment of BCC was assessed in three studies, including two case reports and one clinical study conducted on 43 cases (both adults and children). In the aforementioned studies, irradiation of 33 to 200 J/ cm2 with a density between 40 and100 mW/cm2 was applied for approximately 10 min. ALA (2.5 to 20%) and MAL (160 mg/g) were used as a photosensitizer. The number of treatment sessions was between

two and seven. Final improvement using PDT for BCC treatment ranged between 56.3%% and 100%. Side effects included transient pain and selective phototoxicity with rapid healing. Recurrence has been reported only in one child.

The other studies assessed PDT on the treatment of cutaneous diseases including leishmaniasis (success treatment rate of 93.5%-100%), tinea capitis (success treatment rate of 46%-100%), Xeroderma pigmentosum (XP) (success treatment rate of 0-100%), Langerhans cell histiocytosis (LCH, success treatment rate of 100%), Lymphomatoid papulosis (success treatment rate of 100%), and Bowen's disease (success treatment rate of 100%).

3-1. Risk of bias in outcomes

Since the entered studies varied in terms of type and even included case reports and case series due to the limited data on our subject, we could not provide the quality assessment for all papers. The risk of interventional and RCT bias was assessed in six domains based on the Cochrane guidelines. Other than bias in the domains of sequence generation, allocation concealment, and blinding, in which the risk of bias was high, a low risk of bias was observed in other domains. The assessment results regarding the risk of bias in interventional studies are presented in **Table 2** and **Fig. 2**.

Table-2: Quality assessment of studies entered in the review

Author (years) Reference	Sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective reporting	Other sources of bias
Papageorgiou et al. (24)	No	Yes	No	Yes	Yes	Unclear
Tzung et al. (25)	No	Yes	No	No	No	No
Schroeter et al. (19)	Yes	No	No	No	No	No
Morton et al. (27)	No	No	No	No	No	Unclear
Rojanamatin et al. (28)	No	No	No	Unclear	Yes	No
Hörfelt et al. (29)	Yes	Yes	Yes	No	No	No
Asilian et al. (30)	Yes	No	No	No	Yes	No
Hörfelt et al. (31)	No	No	No	Unclear	No	Unclear
Loncaster et al. (32)	No	No	No	No	No	No
Barolet et al. (34)	Yes	Yes	Yes	No	No	No
Pinto et al. (37)	No	Yes	Yes	No	No	Unclear
Ma et al.(15)	No	No	No	No	No	Unclear
Tao et al.(42)	No	No	No	No	No	No
Tao et al. (43)	No	No	No	No	No	No
Pariser et al. (45)	Yes	Yes	Yes	No	No	No
Li-Qiang et al. (47)	No	No	No	Unclear	No	Unclear
Ahmed Abdul Latif et al. (16)	Yes	No	No	No	No	No
Nassar et al. (17)	No	No	No	No	No	No
Khalaf et al. (49)	No	No	No	Unclear	No	Unclear
Borgia et al. (18)	Yes	No	No	No	No	No
Abdullah et al. (54)	Yes	Yes	Yes	No	No	No
Chun et al(51)	No	No	No	No	No	No
Zhang et al. (52)	No	No	No	No	No	No

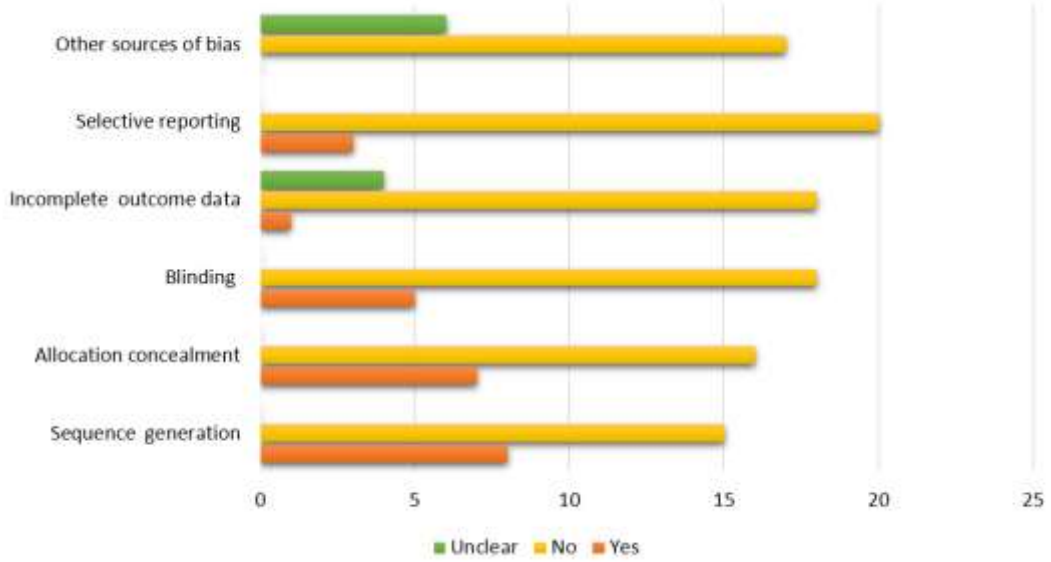

Fig. 2: Quality assessment of the RCT in interventional studies

4- DISCUSSION

4-1. Effect of PDT on the treatment of acne vulgaris

There are reports on the inactivation of P. acnes by relatively small doses of broadband near-UV radiation, based on in vitro evidence (25). Blue visible light around 400-420 nm is absorbed by the predominant porphyrins produced by P. acne (55, 56). Photodynamic stimulation of porphyrins stored in the Cutibacterium acnes and singlet oxygen production has been observed by blue light at 415 nm (57). Moreover, blue light can induce intracellular pH alterations and bacterial damage in P. acnes (58). Papageorgiou et al. reported that using a cumulative blue light dose of 320 J cm22 and blue plus red light radiation improved the success rate of treatment in 45% and 7% of patients with acne, respectively. They concluded that the antibacterial and anti-inflammatory action of blue light and red light may act synergistically in improving acne (24).

Moreover, the anti-inflammatory action of red light has been proven through the promotion of cytokine release from macrophages (59). It seems that red light exerts its therapeutic effects by deep and direct penetration into tissues and targeted sebaceous glands (60). Some evidence indicates the better effects of red light alone compared to blue light which could be attributed to the greater depth of red light penetration. Moreover, it seems that the sensitivity of P. acnes to red light is higher than that to blue light (29). Light causes the formation of singlet oxygen and reactive radicals by exciting the porphyrins. This phenomenon leads to photoinactivation of P. acnes and can explain the improvement in the patients treated only by PDT without the use of photosensitizer.

Treatment parameters of ALA suggested in the literature for the treatment of acne included: concentration between 2.5% and 20 %, incubation time from 1 to 3 h, and red light irradiations with dosimetry of 72–126 J/cm^2 (one to four sessions every two weeks). ALA–PDT has been used for the treatment of acne due to the ability of ALA to penetrate sebaceous glands and increase protoporphyrin IX (PpIX) synthesis. It has been proposed that inducted ALA absorbs red light during photoactivation and leads to the formation of singlet oxygen and reactive radicals, an increase of

endogenous PpIX synthesis, and consequent destruction of the pilosebaceous unit (61). Moreover, red light has been suggested to enjoy anti-inflammatory properties due to its effect on the cytokine release from macrophages and stimulation of fibroblast proliferation, which directly affect wound healing (62).

It is difficult to draw conclusions on the effectiveness of different forms of PDT due to the use of various parameters, including different wavelengths, light dosimetry, skin preparation, and type of photosensitizer, with various concentrations and times of incubation in the literature. The provision of a clear guideline with modification of the aforementioned variables could help improve the efficacy of PDT and decrease its side effects. However, there is still no agreement on how to perform PDT for acne treatment and no consensus on the use of blue or red light sources. Some evidence supports the fact that high-intensity red light has a deeper penetration than blue light sources in the activation of porphyrins in sebaceous glands and sebaceous gland destruction and causes a longer recovery time for acne (63). However, due to the dearth of histological findings, the data could not be generalized to all patients.

The majority of studies manifested that PDT is a well-tolerated approach with no remarkable adverse events. Adverse effects of topical ALA-PDT may be related to the concentration of the photosensitizer, as well as the light source and dosage. This side effect was lower in the study conducted by Barolet et al., which might be attributed to the low-level light sources (LED) (34). It should be noted that although side effects (e.g., swellings and erythema after treatment) caused by other PDT light sources such as IPL and Pulsed Dye Lasers (PDL) have been more intense, they are not very dangerous (31). The incidence of permanent injuries including ulceration and scarring is very rare (63).

4-2. Effect of PDT on the treatment of facial flat warts

Flat warts, filiform warts, and plantar warts caused by HPV are common. Most commonly, flat warts appear localized on the face of children and adolescents in the age range of 6 -15 years with a prevalence ratio of 5.1:1, and warts were observed in 2/3 of cases (64). The treatment of cutaneous viral warts due to FFWs is very hard, especially when warts involve sensitive sites such as the face in children. Several immunotherapeutic agents have been introduced as an effective treatment for plane warts; however, they are associated with local reactions, such as pain, burning, blistering, edema, erythema, and immunologically induced lymphangitis, as well as compartment syndrome in rare cases (65, 66).

Some evidence confirmed decreased HPV viral loads and risk of recurrence by PDT compared to other therapeutic approaches (67). In HPV-infected cells, exogenous ALA and its derivatives may induce selective accumulation of PPIX; and light activation of PPIX could lead to viral inactivation via cell necrosis and killing of the infected keratinocytes via cytotoxic radicals and induction of T lymphocyte-mediated immune response (68, 69). PDT helps to destroy HPV-infected keratinocytes and inactivates non-enveloped viral particles, which probably act via binding PS molecules to the viral surface glycoproteins (23). The study conducted by Mao et al. confirmed the efficacy of PDT on flat warts after three or four treatment sessions at a one-week interval in two of the three patients treated with a combination of 20% ALA and LED (23). PDT could be used as an effective approach in the treatment of plane warts, especially in patients with immunosuppressive conditions and/or on immunosuppressive medication or patients

with hypersensitivity to candida antigen. Moreover, it could be used in children with a fear of needles.

We found three interventional clinical trials on the effect of PDT on children with FFWs (16-19) and only two of them were focused only on children (16, 18), while the use of PDT in the treatment of children with condylomata acuminata was studied in two case reports (70). Since the conventional treatment approaches for condylomata acuminata in children can be painful and recurrent, ALA-PDT has been introduced as an appropriate technique. For instance, a nine-year-old girl with condylomata acuminata was treated with 20% ALA in combination with laser light with minimal adverse reactions and without recurrence for six months (22). In another study, Yin et al. reported successful treatment of a two-year-old boy with condyloma acuminatum using ALA-PDT (20). Only one study was found on the use of photodynamic therapy for plantar warts in adults and children. The treatment success was estimated at 88%. Younger patients had more clearance and total clearance. Moreover, no higher clearance has been reported in patients older than 45 years compared to younger cases. Moreover, the findings indicated that mean treatment time (19 m versus 16 m) was related to better clearance. Complete clearance was not related to mean energy, duration of the warts, and the number of treatments (19).

Although it has been claimed that Conventional Photodynamic Therapy (C-PDT) can help to kill different bacteria, fungi, and viruses, it has some side effects, such as pain during illumination, excessive treatment duration, the need for dedicated equipment, and limited patients' adherence; it seems that the approach is not applicable in children (71). The activation of the topical photosensitizer by exposure to natural daylight, such as Daylight Photodynamic Therapy (DL-PDT), has been introduced as an appropriate approach that does not need preliminary occlusion. This approach can be performed in the outdoor setting and takes less time. In the new method, the topical photosensitizer is induced by exposure to natural daylight. The main advantages of the approach are the low cost and the lack of side effects, such as pains beyond the tolerance of children (21).

4-3. Effect of PDT on the treatment of linear porokeratosis

Porokeratosis has been introduced as a genetic disorder characterized by clonal proliferation of keratinocytes. Linear porokeratosis is a rare type of porokeratosis, which is common in children and may be exacerbated by immunosuppression and lead to squamous cell carcinoma or basal cell carcinoma (72-74). One study was conducted on the effects of PDT for the treatment of porokeratosis in adults with disseminated superficial actinic porokeratosis; however, no treatment response was observed (72), and other evidence rejected the results (73). The treatment of linear porokeratosis has been very difficult and various treatment modalities have failed. The contradictory results of the use of PDT are possibly related to the thickness of the stratum corneum in various patients. The conventional treatment of porokeratosis is topical imiquimod, with an unclear mechanism of action. It probably acts as a toll-like receptor agonist and facilitates the secretion of proinflammatory cytokines. The reported cases in the literature have shown the presence of hypopigmentation residual in children treated with topical imiquimod (75). Studies are rare on the application of PDT in the treatment of populations under the age of 18 years with linear porokeratosis. We found only four studies in the literature (all case reports); however, complete remission has been observed in all reports after using MAL-

PDT without serious side effects or recurrence. MAL hydrochloride has been used in all aforementioned reports in a 160 mg/g concentration for 2 or 3 h with an irradiation dosage of 37 J/cm2 for 8 to 9 min (33, 39-41). Since a fixed treatment has been used in all studies, we suggest conducting more clinical trials to ensure the obtained results.

4-4. Effect of PDT on the treatment of port-wine stain

For the first time, GU Ying et al. used PDT in the treatment of PWS (76). During the treatment of PWS by PDT approach, deformed capillary networks containing photosensitizer will be destroyed by irradiation. In the phenomena, sub-dermal extracellular matrices and normal epidermal cells are not harmed since they do not contain photosensitizers. Therefore, the treatment process has been performed without damage to normal tissue both on the surface and around the lesions (77). Although PDL is the gold standard for PWS (78), PDT has been introduced as a potential treatment approach in this regard. Hematoporphyrin monomethyl ether (HMME), as a porphyrin derivative in combination with PDT, has been suggested as an effective treatment in patients with PWS due to targeting destructive effects on lesions' vascular walls. HMME is rarely absorbed by epidermal cells, although it is placed where the speed of its absorption by vascular endothelial cells is high. The light irradiation to the superficial layer generates singlet oxygen and other reactive oxygen species and consequently destroy the deformed capillary network (79). However, due to the dearth of evidence, the adoption of photodynamic therapy for children is challenging (80). In this regard, Zhang et al. reported that two cases of pink PWS were treated with Hemoporfin-mediated photodynamic therapy (HMME-PDT) and a green light LED (535 nm), and any allergic reaction during and after the irritation had been observed two weeks after treatment (46). Li-Qiang et al. used HMME-PDT therapy to treat PWS in children and confirmed its efficacy with minimal complications. They also showed that the approach was more beneficial in the treatment of PWS in the head or neck probably due to the thin skin of these areas compared to extremities. Moreover, they showed a better improvement in younger patients (1-2 years versus 3-14 years old) (47). These findings were confirmed in another study conducted by Khalaf et al., in which both children and adults were treated by HMME-PDT (49). In general, the success rate of HMME-PDT therapy for children with PWS has been estimated to be between 70% and 100%.

4-5. Effect of PDT on the treatment of Basal cell carcinomas

In many types of cutaneous diseases, such as Gorlin syndrome, the use of radiotherapy is contraindicated since the mutation of the PTCH gene leads to increased sensitivity to radiation. Moreover, the BCCs may develop in the penumbra of the treated area. On the other hand, standard treatment includes surgical excision and cryotherapy which may lead to remarkable disfigurement from scarring (32). Routinely, PDT has been used with topically-applied photosensitizer and external light to manage superficial sporadic BCCs. However, its role in the treatment of thick and nodular lesions of Gorlin syndrome is still unclear. Since the use of radiotherapy has been contraindicated due to enhanced radiation tumorigenesis in patients with Gorlin syndrome, Loncaster et al. suggested photodynamic therapy in patients with Gorlin syndrome who developed BCC, while PDT could be used as a simple, repeatable, out-patient approach. This method is associated with minimal skin deterioration. They used topical PDT to treat lesions with a thickness smaller than 2 mm, and lesions with a thickness bigger

than 2 mm were treated with a systemic photosensitizer D/L light delivered by interstitially-placed optical fibers. Ultrasound assessment has been performed in all patients to detect the thickness of lesions and determine the optimum treatment. Treatment success was 56.3% after one year. It seems that the use of a systemic photosensitizer D/L interstitial light helps to treat thick lesions by extending the remit of PDT. Therefore, they concluded that PDT had advantages for the treatment of cutaneous lesions developed by Gorlin syndrome and could replace surgery (32). However, in the aforementioned study, the treatment success was not specified only for children and we found no more studies on the role of PDT in the treatment of children with Gorlin syndrome. Therefore, it seems that further studies need to be performed on this issue.

In this regard, Oseroff et al. introduced ALA-PDT as a safe instrument and well-tolerated approach, which proved to be effective in the treatment of extensive areas of superficial BCCs in three children aged 6, 10 and 17 years (two females and one male).

The overall local control rates were low in the study conducted by Loncaster et al., compared to other studies conducted on adults. However, it is not possible to relate the issue to the age range, since the treatment success rate has not been specified for adults and children separately. Moreover, the pre-treatment lesion thickness and diameter were not reported in other studies; therefore, it is not possible to compare them with those reported by Loncaster et al. In addition, the patients included in the aforementioned study represent a particularly challenging group of patients with Gorlin syndrome who developed multiple BCCs.

4-6. Effect of PDT on the treatment of cutaneous leishmaniasis

In one randomized comparative clinical trial by Asilian et al., 60 patients with cutaneous leishmaniasis were treated with weekly topical PDT and red light (633 nm) at 100 J ⁄cm2 for 4 weeks. Complete improvement was reported in 93.5% of patients and the frequency of improvement was higher in the ALA-PDT group compared to placebo and paromomycin groups. Moreover, a shorter period in all treated lesions was observed in the PDT group compared with the topical paromomycin group. They concluded that four sessions of PDT, once a week, could be an optimal treatment to achieve a high rate of parasitological success (30). In another study (case report) conducted by Knapp et al., the effect of PDT was confirmed on cutaneous leishmaniasis in 13-year-old adolescents (53). We found only two studies on the treatment of cutaneous leishmaniasis by PDT, one case report, and one study conducted on both adults and children. Due to the fact that treatment success rate was not specified separately for adults and children, along with the dearth of studies in this regard, the generalization of the results to other populations should be made with caution. Therefore, future studies should assess the effects of PDT on cutaneous leishmaniasis in children.

4-7. Effect of PDT on the treatment of other cutaneous diseases

PDT has been used for various cutaneous diseases in children; however, due to the few studies (mostly case reports), we could not generalize the data to other populations. In one RCT performed by Abdullah et al. on a population under the age of 18 years, 52 children with tinea capitis were treated with curcumin loaded in nanospanlastics-PDT. Complete clearance has been reported in 46% of patients, and no effects and recurrence have been reported after PDT (54). In a previous case report, we introduced PDT as a beneficial treatment for tinea capitis in

a two-year-old child (48). In addition, four case reports confirmed the positive effects of PDT in the treatment of XP (36), LCH (35), lymphomatoid papulosis (50), and Bowen's disease (44). Future studies should be performed to confirm or reject the obtained results.

5- LIMITATIONS OF THE STUDY

This study has some limitations. Firstly, interfering factors, lack of homogeneity in demographic characteristics of patients (age, gender, and race), and other unknown intervening factors may affect the results obtained in the present study. Moreover, a large part of the data has been extracted from the case reports and case series. The single-center nature of some studies and the high risk of bias in some domains of the quality assessment prevent the generalization of the results to other populations. We found no homogeneous studies to convert this review to a meta-analysis. We suggest that future multicenter-RVT assess the effects of PDT on the treatment of cutaneous disease in the pediatric population due to the insufficiency of data for obtaining definite results. Moreover, we could not exclude studies that included both adults and children due to lack of adequate studies. It was impossible to separate the data related to children and adults in each study, or remove them because in that case, we would have lost a large population of children who were eligible for inclusion in the present study. In addition, due to the lack of studies conducted on large populations, we had to include even case reports in the article. For this reason, in the present study, it was not possible to conduct a meta-analysis. Finally, just when we wrote this study, a similar review article was published in 2022 titled " Photodynamic Therapy for Treatment of Disease in Children—A Review of the Literature" There were two main differences between the present study and the aforementioned one. First, the present study is a systematic review; second, the aforementioned study is not comprehensive enough and does not include all studies focused on Photodynamic in children.

6- CONCLUSION

It seems that PDT has a treatment potential to be used for children with cutaneous disease. In general, high treatment success has been reported for the use of PDT in children with cutaneous diseases, including acne vulgaris, plantar warts, condyloma acuminatum, porokeratosis, PWS, BCCs, leishmaniasis, tinea capitis, XP, LCH, Bowen's disease, and Lymphomatoid papulosis. Due to the existence of non-uniform parameters for PDT treatment, optimization of the treatment protocol is necessary to ensure better results with long-term remission in children with cutaneous diseases (separately for each disease). Moreover, further studies should be performed to establish the optimal interval for subsequent treatments.

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