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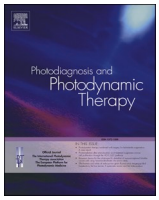

Evaluation of the effectiveness and safety of photodynamic therapy in the treatment of precancerous diseases of the cervix (neoplasia) associated with the human papillomavirus: A systematic review

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ABSTRACT

This study provides an overview of the effectiveness and safety of PDT for the treatment of HPV-associated precancerous cervical conditions and contains recent findings from relevant research studies. A comprehensive literature search of MEDLINE/PubMed, Cochrane Central Library, and Google Scholar was conducted, including analytic epidemiological studies, and 11 papers were included. The narrative synthesis approach was used to summarize the results of the included studies. Studies were critically appraised using The Joanna Briggs Institute (JBI) tool for assessing the risk of bias. The results of the study demonstrate that CRR for HPV remission ranges from 66.7 % to 92.73 %, whereas for CIN1 it fluctuates from 57.1 % to 83.3 %. The frequency of recurrence of the disease ranged from 3.3 % to 8.9 % during the follow-up period of up to 2 years. Adverse events were observed in 8 (66 %) studies and the most common were cervical stenosis, abdominal pain, vaginal pain, and focal edema. Five types of topical and intravenous applications along with lasers of various wavelengths and intensities were mostly used. However, all studies demonstrated relatively similar results. According to the results, PDT has demonstrated favorable outcomes, but no impressive effect on the treatment of CIN. It should be emphasized, that the effectiveness of PDT for the treatment of HPV-associated CIN may vary depending on some variables, including the kind of PDT agent used, the dosage, duration and frequency of PDT administration, the severity and location of the lesions, and the host immunological response.

1. Introduction

The development of uterine cervical neoplasms is mostly caused by oncogenic strains of human papillomavirus (HPV) which are sexually transmitted and highly prevalent [1,2]. Roughly, 20 % of infected women are diagnosed with cervical intraepithelial neoplasia (CIN). CIN classification is divided into CIN1 (mild), CIN2 (moderate), and CIN3 (severe) [3,4]. It generally takes more than a decade for CIN to progress into cervical cancer. Cervical cancer ranks as the fourth most prevalent form of cancer in women worldwide. According to statistics from 2020, cervical cancer was responsible for 604,000 newly diagnosed cases and 342,000 deaths across the world [5]. The overwhelming majority of cervical cancer cases, exceeding 90 %, are linked to HPV [6,7].

Generally, HPV is responsible for most cases of cancer of the head and neck, anus, penis, cervix, oral cavity, and others [8]. This accounts for about 4.5 % of all diagnosed malignant neoplasms in humans. While there are over 182 identified types of HPV, only specific types as 16 and 18 are considered major risk factors for the development of CIN and cervical cancer [9–11]. The reason for the lack of attention from doctors and society towards HPV is that most HPV infections are temporary and can be cleared by the body's immune system. However, this lack of attention may lead to a growing and deadly problem, as each new HPV infection has the potential to become a lifelong, incurable disease if left untreated. Despite significant progress in understanding the mechanisms underlying HPV pathogenesis, there is currently no successful therapy for HPV infection. Research has demonstrated that preventive vaccines have resulted in a decrease in the burden of HPV infection. Nevertheless, not all nations have implemented government-funded

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HPV vaccination programs to protect young individuals [12].

Traditional therapeutic approaches for managing CIN are often invasive and can be categorized into two main groups: destructive methods such as laser evaporation, cryodestruction, and diathermocoagulation that are aimed at eradicating the abnormal tissue, and pathological tissue removal techniques that involve laser, electrosurgical, or surgical excision. While various treatment methods, such as cryosurgery, large loop excision of the transformation zone, cold-knife excision, laser ablation, and electrocautery have demonstrated high success rates, there is no consensus on the best approach for managing CIN [13–15]. The most prevalent side effects of these treatments include hemorrhage, damage to underlying tissues resulting in the formation of rough surfaces, and stenosis or constriction of the cervical canal. Alterations in the anatomy of the cervix uteri can result in functionality loss. This can cause a decrease in cervical secretions, which in turn can reduce the likelihood of conception, increase the risk of spontaneous abortion, lead to a rise in perinatal mortality, and hinder normal delivery [16–18]. Undoubtedly, finding the most effective way to manage CIN demands the exploration and implementation of new therapeutic approaches while preserving the functional integrity of the affected organ. Thus, one potential solution that can fulfill these criteria is Photodynamic Therapy (PDT).

PDT is a treatment approach that is non-invasive or minimally invasive and has demonstrated potential in the management of cervical neoplasia. PDT is a treatment method that employs a photosensitizer (PS) to selectively kill cells, often cancer cells, by activating them inside the body using laser light [19]. The use of various photosensitizers that are selective towards specific tissues combined with laser irradiation that is focused on the lesion area and the short half-life of the cytotoxic species generated in the process helps ensure that the phototoxic damage is primarily restricted to the lesion, sparing normal surrounding tissues. As a result, PDT causes less damage to normal tissues than conventional treatments such as surgery, radiation therapy, or chemotherapy, and thus, represents a promising alternative therapeutic approach for managing CIN [20,21]. Moreover, PDT can stimulate the human innate immune system, which in turn may be salutary in the treatment of HPV infections [22,23].

Although the effects of PDT have been studied since the end of the last century, its impact on CIN is still not widely and accurately understood. Several systematic reviews have already investigated the safety and efficacy of PDT for CIN and found positive trends. However, to date, many of the papers included in the reviews have relatively outdated data [21,24].

We are investigating the following questions: what is the overall effectiveness and safety profile of PDT in the treatment of precancerous lesions of the cervix associated with HPV compared to other treatments or placebo? What is the long-term effectiveness of it? Are there any differences in the effectiveness or safety of photodynamic therapy in subgroups of patients based on factors such as age, HPV status, severity of precancerous lesions, treatment dosage, or treatment duration?

The study aims to evaluate the effectiveness and safety of PDT in the treatment of precancerous diseases of the cervix associated with human papillomavirus (HPV).

2. Methods

The systematic review in question follows the guidelines set forth by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) for accurately reporting reviews. The review conducted a comprehensive search for all pertinent articles examining the effectiveness and safety of photodynamic therapy (PDT) in managing cervical intraepithelial neoplasia (CIN) associated with cervical human papillomavirus (HPV) infection. To conduct this systematic review, we firstly, first PICO indicators where P (population) = female with HPV-associated CIN, I (intervention, exposure in our case) = PDT, C (comparison group) = placebo groups or other treatment methods, and O (outcome) = clinical effectiveness and safety. The study protocol has been registered in PROSPERO: CRD42023426056.

2.1. Search strategy

Cochrane Central Library, PubMed, and Google, Scholar databases were searched to identify papers related to the study topic. The search process lasted from January until April 2023. There are three main terms combination were utilized: “Cervical intraepithelial neoplasia OR Cervical cancer”, “Photodynamic therapy or PDT”, and “human papillomavirus OR HPV”, used in searching in databases. All articles were selected from electronic full-text academic journals in English only. Only studies that were published last 10 years were included in the analysis.

2.2. Selection criteria

The systematic review utilized the following inclusion criteria: types of study designs, such as case-control studies, cohort studies, and randomized controlled trials; cases involving cervical dysplasia, squamous intraepithelial lesions, or cervical intraepithelial neoplasia confirmed by biopsy and/or cytology; application of PDT as a mono-therapy or in conjunction with another therapy; all wavelengths and light sources; studies with or without comparators; all clinical outcomes, including but not limited to the HPV eradication rate (HER), the complete response rate (CRR) of lesions, and any adverse effects; and a minimum follow-up period of more than three months. Additionally, we consider dimensions such as country, age, and CIN grade.

After selecting papers three researchers independently reviewed all of them by titles and abstract and obtained relevant papers. In the event of any discrepancies between the reviewers, they were resolved through discussion and consensus to reach a final decision. The relevant data was entered into a spreadsheet for comparative analysis, and if all reviewers agreed, the study was included in the Mendeley data pool and some duplicated articles were extracted through that tool. During the full-text screening, we excluded studies that did not meet the criteria we had previously specified for inclusion.

2.3. Data extraction

The information from the included articles was gathered by three researchers independently using a previously designed data collection form. The following data were extracted from each study: the first author, country, study design, number of patients, median age, follow-up period, type of CIN, intervention, measurement tools, and results with CRR. In the event of any discrepancies between the reviewers, they were resolved through discussion and consensus to reach a final decision.

Joanna Briggs Institute (JBI) tool was applied by three researchers independently to estimate the risk of bias in each separate study. Domains like sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other threats to validity were considered to determine the risk of possible biases. The scale for evaluation consists of three levels of bias: high risk of bias indicates probable bias that seriously weakens confidence in the results if one or more key domains were assessed to be negative. For a low risk of bias which is unlikely to alter the results, all key domains should be positive. If domains raise some doubt about the results and the risk of bias, the last one will be assessed as unclear.

2.4. Data synthesis

The narrative synthesis approach was used to summarize the results of the included studies. We described the safety and efficacy of photodynamic therapy for CIN based on the information provided in the studies.

3. Results

The record identified 7059 papers through database search, namely 398 in Pubmed, 6630 in Google Scholar, 31 in Cochrane central library, and 2 by citation search. 148 papers were excluded due to duplication. 6802 studies were removed because of not appropriate study design and publication date, some papers represented study protocols and only contained plans for future studies conducted, some papers were either systematic or meta-analyses, and some papers had no full text, therefore they were also excluded. The rest 109 papers went for full-text analysis. In 98 out of 109 studies did not consider CIN, some focused only on pharmacokinetics, lacked full text, or did not have an appropriate study design. In total, 11 studies were considered for qualitative synthesis. The graphical representation of the exclusion process is available in Prisma Flow Chart (See Fig. 1).

The main results of this study are demonstrated in Table 1. The total sample size of included studies ranged from 20 to 262. The majority of studies, namely 5, were undertaken in China, 2 studies each in Korea, Germany, and Brazil, and one in Japan. In terms of study design, most of the studies were prospective or retrospective, and only a few were randomized controlled trials (RCTs). Regarding PDT applications, the studies used 5 types of different photosensitizing agents and light sources. For example, Liu et al., Li et al., Mizuno et al., Fu et al., Chen et al. and Zhang et al. used 10 or 20 % 5-aminolevulinic acid (ALA) thermogel with a 632.8 nm, 633 and 635 red light lasers [25–30], and Inada et al. used 20 % Methylaminolevulinate (MAL) cream with 630 nm LEDs at 80–180 of fluency [31], while Hillemanns et al. in their 2 clinical trials utilized Hexa-aminolevulinate (HAL) as vaginal suppositories or hydrochloride [32,33], and Choi et al. used photogem intravenously [34]. In terms of assessment methods, most studies used histopathology, HPV DNA testing, and colposcopy to evaluate treatment outcomes. However, some studies also used cytology and autofluorescence visualization, which may provide additional information about the effectiveness of PDT. The follow-up periods varied across the studies, ranging from 3 to 120 months.

The CRRs varied across the studies and may be influenced by differences in study design, PDT applications, and assessment methods. Regarding the treatment outcomes, most studies reported a high complete remission rate (CRR) for CIN and HPV infection following PDT treatment. The results of the study demonstrate that CRR for HPV remission ranges from 66.7 % to 92.73 %, whereas for CIN1 it fluctuates from 57.1 % to 83.3 %, however, Hillemans found no statistically significant result in the CIN1 and CIN1/2 compared to the placebo group [33]. As for CIN2 and CIN3, the total CRR is between 95 % and 100 %, except for the data from Mizuno et al. [27], since they showed all the CIN results in one CRR, which was equal to 70.6 %, and in the context of grading CIN, an improvement in grade was observed in 15.7 % of the total cases studied, which occurred when the grade decreased from CIN3 to CIN2 or CIN1, or when it decreased from CIN2 to CIN1.

Whereas RCTs are generally considered to provide higher-quality evidence than observational studies, as they minimize the risk of bias and confounding factors [35], the results of some of them are described

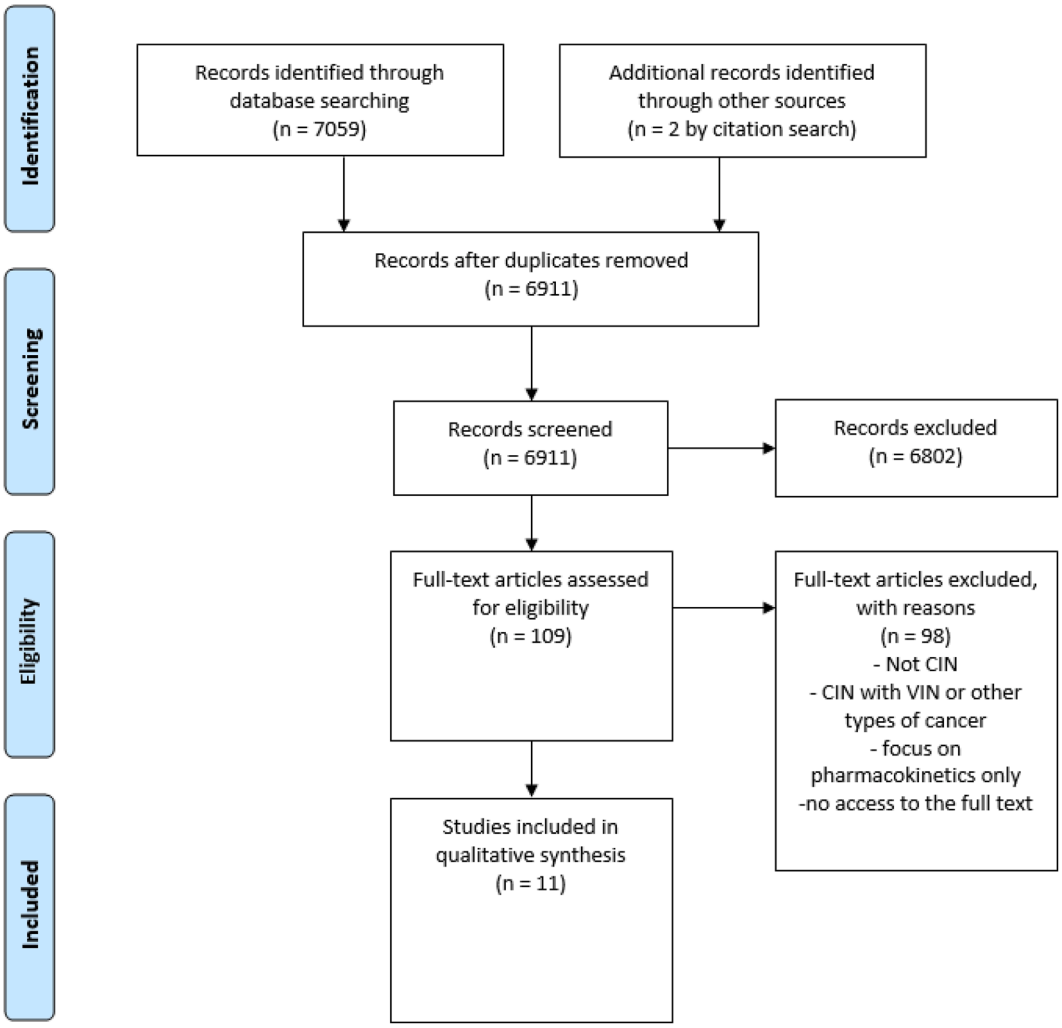

Fig. 1. Prisma flow diagram.

Table 1
Characteristics of included studies.

#	Authors, year	Country	Study design	Number of patients	Median/ mean age	Disease	Intervention	Assessment	Follow-up period, months	Results, CRR	Adverse reactions
1	Fu et al. [28]	China	Prospective study	76(TG – 39, CG - 37)	TG: 30 (19–61) CG: 31 (22–59)	CIN1	TG - topical PDT with 10 % ALA thermogel (Shanghai Fudan–Zhangjiang Bio-Pharmaceutical Co., Ltd.) with a 635 nm diode laser (LD600-C; Wuhan Yage Photo-Electronic Co. Ltd, Wuhan, China), light irradiation of 100 J/cm2. Duration: 3 times with 2 weeks interval CG – no treatment	TCT and colposcopic histopathology biopsy, HR-HPV DNA	3 & 9 months (Feb2012 – Feb2014)	• 3 month follow up period for HR-HPV remission: CRR=64.10 % in TG vs 24.32 % in CG (x^2 = 12.152, $P < 0.01$) • 9 month follow-up for HR-HPV remission: CRR=76.92 %% in TG vs 32.40 % in CG (x^2 = 15.202, $P < 0.01$) • 9-month follow-up for CIN1 conversion: 83.33 % in TG vs 0 % in CG (X^2 = 7.639, $P < 0.001$).	Minor local toxicity:- burning sensation;- vaginal discharge.
2	Liu [25]	China	Controlled CT	110	28 (mean age) (24–46)	CIN1	OG – topical PDT with 20 % 5-ALA; He-Ne laser with 632.8 nm red light, 100 j/cm2; CG – high-frequency electric ion operating treatment. Duration: 4 times with 1 week interval; ALA: 3 h before; PDT: 40–50 min	Colposcopy, TCT, HPV-DNA	6 & 9 months (Jan2013 – Sep2014)	• The 6-month follow-up period for HR-HPV RR: 81.81 % in OG and 52.73 % in CG (x^2 = 4.9381, $P < 0.05$); • The 9-month follow-up period for HR-HPV RR: 10.91 % in OG and 7.27 % in CG (x^2 = 2.1164, $P < 0.05$); • Total RR of HR-HPV DNA: 92.73 % in OG and 60.0 % in CG (x^2 = 4.2615, $P < 0.05$)	–
3	Choi [34]	Korea	Retrospective study	59	30.4	CIN2, CIN3, CIS, AIS with CIN3	Photogem intravenously (Moscow, Russia-2 mg/kg) and red laser light with a wavelength of 630 nm (CERALAS; Ceram Optec GmbH, Bonn, Germany), 150 J/cm2. Gr1: only PDT Gr2: PDT + LEEP/Cone Gr3: PDT within 3 months after LEEP/Cone Gr4: PDT after 12 months after LEEP/Cone due to CIN recurrent Duration: Photogem was administered 48 h before laser.	Biopsy, HPV DNA	6–120 months (median: 55.2) (Sep2000 – Aug2011)	CRR of HR-HPV DNA: • 3-month follow-up period: 89.8 % (44/49); • 12-month follow-up period: 87.0 % (40/46); Total CRR of PDT at 12 months follow up: 98.1 % (52/53)Gr1: CIN2: 100 % (2/2), CIN3: 100 % (6/6), CIS: 80 % (4/5). CRR = 100 % (13/13)	15.3 % (9/59)- photosensitivity grade1/2 – 7; - photosensitivity grade3 – 1;- cervical stenosis – 1
4	Hillemanns [32]	Germany	Prospective, randomized, double-blind, placebo-controlled, Phase IIa	59	30.2 (21–55)	CIN1	TG – HAL vaginal suppositories 100 mg; red coherent light with h wavelength of 633 nm (Biolitec, Germany), 50 J/cm2 CG – placebo vaginal suppositories+PDTfollow-up only. Duration: 2 times with 1 month interval; HAL/placebo: 5 h before; PDT: 17 min	Colposcopy,cytology and HPV testing	3 & 6 months	CRR of CIN1 after 6 months: • TG: 57,1 % (20/35 PP) • CG: 25.0 % (4/16 PP) [placebo+PDT: 40.0 % (4/10) and follow-up group: 0 % (0/6)], p = 0.040 CR of HPV: • TG: 73.3 % (11/15 PP)	TG: 31.9 % (15/47) CG (placebo+PDT): 8.3 % (1/12) CG (follow-up): 0 %

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Table 1 (*continued*)

#	Authors, year	Country	Study design	Number of patients	Median/ mean age	Disease	Intervention	Assessment	Follow-up period, months	Results, CRR	Adverse reactions
										• CG: 50 % (5/10 PP) [placebo+PDT: 28.6 % (2/7) and follow-up group: 100 % (3/3)], $p = 0.397$	
5	Hillemanns [33]	Germany	Double-blind randomized placebo-controlled, dose-finding study, Phase IIb	262	27 (18–60)	CIN1, CIN2	topical treatments of HAL hydrochloride 0.2 %, 1 %, 5 % TG1: HAL 5 % TG2: HAL 1 % TG3: HAL 0.2 % CG: placebo Duration: HAL/placebo: 5 h before; automatic illumination for 4.6 h.	Colposcopy, Biopsy, HPV DNA PCR	3 & 6 months	There is no statistically significant result in the CIN1 and CIN1/2, also in HAL1 % and HAL0.2 % compared to the placebo group. CRR in CIN2: 3 months: TG - 95 % (18/19), Placebo – 57 % (12/21), $p = 0.009$ 6 months: TG - 95 % (18/19), Placebo – 62 % (13/21), $p = 0.021$ CRR in HR-HPV: 3 months: TG - 83 % (5/6), Placebo – 0 % (0/6) 6 months: TG - 83 % (5/6), Placebo – 33 % (2/6) Dose-related response in CIN2+HPV eradication: 6 months: HAL5 % - 84 % (16/19), HAL1 % - 48 %. (14/29), HAL0.2 % - 42 % (8/19), Placebo – 38 % (8/21)	HAL5 % - 54 % Others – 31–34 % Mostly: - vaginal discharge; - local discomfort; - spotting
6	Park [36]	Korea	retrospective study	22 patients, 50 cases 20 with HPV	31.2	CIN2, CIN3, ICC	TG: photogem sensitizer and 632 nm diode laser (Biolitec, Ceralas, Germanphotoprintfrin sensitizer and 630 nm diode laser (Diomed, Cambridge, UK), 240 J/cm2. Duration: 2 cycles with 1- or 2-months interval (every cycle with 2 days interval)	cytology, HPV DNA test, cervicography and histology, Pelvic CT	12–108 months (Oct2005-Dec2011)	CRR in CIN = 95 % Progressive disease: 4.5 % Recurrence: 4.5 % (18 months)	- focal edema - burning sensation
7	Inada [31]	Brazil	RCT	56 patients with CIN1; 10 with CIN 2/3; 14 patients for the placebo group	CIN1: 25 (15–57); CIN2/3: 30 (18–49)	CIN1, CIN2/3	TG: 20 % MAL cream application and CerCa 150 System leds emitting at 630 nm, 80–180 J/cm2 of fluency; CG: only cervix illumination ($n = 8$) or only MAL cream application ($n = 6$) Duration: 2 times with 1-week interval; MAL: 1 or 3 h before PDT.	Colposcopy Pap smear test autofluorescence visualization	12&24 months (CIN1: Apr2013-Oct2015-Jul2017; CIN2/3: Apr2015-Sep2016-Dec2018)	42 of 56 patients with CIN1 had CRR=75 % for 1 (12.5 %) and 2 (62.5 %) years of follow-up period; CIN1 remained in 5.4 %, CIN2 progression in 8.9 %, CIN1 recurrence in 8.9 % within 2 years after PDT. For CIN 2/3 patients, CRR=90 % after 1 (30 %) and 2 (60 %) years of follow-up period. Placebo group: abstention - 28.57 % and lesion persistence - 14.3 %; The	–

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Table 1 (*continued*)

#	Authors, year	Country	Study design	Number of patients	Median/ mean age	Disease	Intervention	Assessment	Follow-up period, months	Results, CRR	Adverse reactions
8	Li [26]	China	Prospective study	77	43 (24–69)	CIN1	TG: 20 % 5-ALA and LED- IB type, wavelength of 633 nm (Wuhan Ya Daylight Electric Technology Co. LTD) and 80 J/cm2. Duration: 3 or 6 times with 1 week interval; PDT: 30 min	thin prep cytology test(TCT) colposcopic histopathological biopsy	3&6&12 months	CR - 57.14 % for 1 and 2 years of follow-up period CRR in HR-HPV: 3 months = 75.32 % (58/77), 6 months = 80.52 % (62/77), 12 months = 81.82 % (63/77). CRR of CIN1 at 6 months follow up = 88.31 %, at 12 months follow up = 94.81 %	75 % - vaginal burning - stinging sensations, - vaginal discharge - pruritus vulvae.
9	Mizuno [27]	Japan	a clinical trial, Prospective study	51	39 (21–50)	CIN1, CIN2, CIN3	20 % 5-Aminolaevulinic acid (5ALA), 633 nm light, 1000–150 J/cm2 Duration: 2 times with 1–2-week interval	Uterine cytology, colposcopy-directed biopsy, and histology	The median obs period was 37 months (2012–2017)	Positive effects = 96.1 % CRR = 70.6 % CR of HPV = 79.4 % Recurrence = 3.7 % (1/51)	- vaginal discharge (96.7 %) - abdominal pain (7.8 %) - vaginal pain (1.9 %)
10	Chen [29]	China	Retrospective analysis	115 (EG: 62 CG: 53)	TG: 36.23 CG: 35.71 (25–45)	CIN1	5ALA and LD600-C photodynamic therapy instrument (Wuhan Yage Optic Electronic nic Technique Co., Ltd.) 635 nm red light wave at 80 mW/cm2. Duration: 3 times with 1–2-week interval; ALA: 3–4 h before; PDT: 30 min	liquid-based cytology test (LCT), high-risk HPV (Hr-HPV) test, colposcopy, and biopsy	(Oct2020-Jun2021)	After 6 months of follow-up: the EG = HPV CR - 79.0 %, LSIL reversal rate - 80.6 %, CG = HPV CR - 62.3 %, LSIL reversal rate - 64.2 % ($P<0.05$)	4.8 % - colporrhagia - menstrual abdominal pain - colpitis
11	Zhang [30]	China	Retrospective analysis	83 (33–ALA-PDT 35 – follow up 15 – a repeat cervical conization)	36.12 (24–62)	CIN1, CIN2 CIN3	20 % 5-ALA thermosensitive gel (Shanghai Fudan-Zhang Jiang Bio-Pharmaceutical Co, Ltd) and light irradiation at 635 nm and 100 J/cm2. Duration: 6 times with 1 week interval; ALA: 3 h before; PDT: 30 min	TCT cytology, colposcopy, HPV-DNA testing	24–52 months (Jan2015 – Dec2018)	6 months after ALA-PDT: Residual lesion rate – 9.1 % (3/33), $p = 0.004$ The HPV clearance rate – 66.7 %, $p = 0.01$ Recurrence rate – 3.3 % at 2 years follow up, $p = 0.021$	–

below. Liu et al. performed a controlled clinical trial on 110 participants using PDT with 5-ALA and high-frequency electric ion operating and found a CRR of 92.73 % for HPV in the observational group and 60.0 % in CG (x2 = 4.2615, $P < 0.05$) [25]. Meanwhile, Hillemanns et al. conducted 2 research in 2014 with follow-up periods of 3 and 6 months, first one was a Phase IIa double-blind randomized placebo-controlled study on 59 patients where CRR for CIN1 after 6 months was 57,1 % in TG, 25.0 % in CG, and complete response of HPV was 73.3 % in TG and 50 % in CG [32]. The second research was a Phase IIb Double-blind randomized placebo-controlled, dose-finding study on 262 participants using topical treatments of HAL hydrochloride and found a significantly higher CRR in the HAL 5 % group compared to the placebo group after 6 months follow-up: TG - 95 % and CG – 62 %, $p = 0.021$ in CIN2 treatment and TG - 83 %, Placebo – 33 % in HR-HPV eradication [33]. In addition, Inada et al. conducted an RCT on 56 patients with CIN1 and 10 with CIN2/3 using PDT with MAL cream and found a CRR of 75 % for CIN1 and 90 % for CIN2/3 after 1 and 2 years of follow-up [31].

The frequency of recurrence of the disease ranged from 3.3 % to 8.9 % during the follow-up period of up to 2 years. There is a difference in the CRR between people who have CIN2/3 and those who have CIN1, with the CRR being higher in people who have the more severe form of CIN (CIN2/3) compared to those with CIN1.

Concerning the safety of PDT in terms of adverse reactions, scientists note a minimal rate of photosensitivity of various degrees, cervical stenosis, focal edema, abdominal pain, vaginal pain, coprophagia, and colpitis. The most common side effects were vaginal discharge (up to 96.7 % [27]), burning/ stinging sensations and pruritus vulvae (up to 75 % [26]), local discomfort, and spotting (up to 54 % [33]).

4. Discussion

In recent years, there has been a rise in the occurrence of CIN, particularly in young women, which has had a significant impact on women's reproductive health. CIN is a reversible and prolonged precancerous condition that occurs before the development of cervical cancer [37]. Timely and effective intervention could significantly reduce the incidence of cervical cancer. Women with a history of CIN are 20 times more likely to develop cervical cancer than healthy women [38]. Although CIN1 typically does not require treatment, women with this condition are advised to undergo long-term follow-up, which can cause anxiety and lead to a high rate of follow-up dropout. In some patients, CIN1 can progress to high-grade lesions. The probability of HPV16/18 converting to CIN1 within a year has been reported to be 9 %, while only 7 % of CIN1 progresses to CIN2/3 within a year [39]. Therefore, it is advisable for patients with CIN1 to receive early intervention to reduce the risk of cervical cancer.

Thus, the results of this systematic review demonstrate that PDT is a remarkable alternative approach to HPV-associated CIN treatment. Tao et al. came to the same conclusion about PDT as we did about treating CIN, and they achieved a preliminary combined CRR of 80.5 %, which shows a notable therapeutic regression of CIN [21].In a meta-analysis conducted by Zhang et al., 48 out of 77 patients (62.3 %) experienced CR regarding HPVDNA isolation during follow-up for 3 months compared to 22 out of 74 (29.7 %) patients who received a placebo or only follow-up. Thus, PDT contributed to the elimination of HPV (OR=3.82, $P = 0.00002$) [40]. In addition, Unanyan et al. also conducted a systematic review with meta-analysis, where PDT demonstrated a statistically significant result in the CIN and cervical cancer regression compared to the control group (HR=1.72, $P = 0.0001$) [41].

The long-term effectiveness of PDT in the treatment of HPV-associated CIN was observed in four studies. According to the results of Park et al. recurrence of CIN was 4.5 % for 18 month follow-up period [36], while Mizuno et al. detected CIN lesion recurrence in 5 patients, in 4 participants (57.1 %) who continued to be HPV-positive after treatment and in 1 participant (3.7 %) with a change in HPV status before and after PDT from positive to negative [27]. The follow-up period of about 2 years was estimated by both Inada et al. and Zhang et al. with results of 8.9 % and 3.3 %, respectively [30,31]. Additionally, some studies published before, also, showed positive results. For instance, Muroya et al. detailed that they have treated 131 patients using PDT and 127 (96.9 %) of them reach CR, and during 10 years from that, no recurrence cases have been monitored [42].

The safety of PDT in HPV-associated CIN treatment can be considered in two aspects as adverse events and pregnancy outcomes. Adverse events are described in 8 of 12 studies (66.6 %) and all of them reported mild adverse events and fast recovery after therapy. Vaginal discharge and burning sensation are the most common effects, which coincide with the results of Tao et al. [21]. Also, several studies have investigated and analyzed the effect of PDT on fertility. Hence, all of them concluded that PDT is suitable for women who want to maintain fertility, as it does not cause damage to the anatomical structures [26,29,30,33,36]. While traditional surgical treatments for CIN can damage the stroma of the cervix, which can lead to infertility, miscarriage, or premature birth [43, 44].

Mainly five types of photosensitizers were used in the study such as topical 5-ALA thermogel (50 %), HAL vaginal suppositories (8.3 %), HAL hydrochloride (8.3 %), MAL cream (16.7 %), and intravenous photogem (16.7 %). The most commonly used is the 5-ALA thermogel. According to the results, 5-ALA is the most commonly used photosensitizer, which utilized 633 or 635 nm wavelengths at 80, 100, or 150 J/cm2 and ended up with the results of HPV elimination from 66.7 % to 92.73 % in experimental groups versus 32.40−62.3 % in control groups. HAL is an improved ester of ALA and is a more powerful lipid-soluble derivative. Early trials using topical photosensitizer had CR rates ranging from 33 % to 71 %, which were somewhat disappointing [45]. In our study, HAL vaginal suppositories 100 mg with a light of 633 nm and 50 J/cm2 showed a result of HPV CR 73.3 % in TG versus 50 % in CG using a placebo (28.6 %) or only follow-up (100 %). In a paper Hillemann et al. revealed the dose-dependent effectiveness of PDT in CIN 2 [32]. The HAL was administered in hydrochloride form with 5 %, 1 %, and 0.2 % with 629 nm red light of 100 J/cm2 dose. In the result, at the 6-month follow-up, CRR in CIN2 with HPV was 83 % in TG and 33 % in CG. The intravaginal device that gynecologists employed might be removed by the patients on their own. It permits PDT to be performed on an outpatient basis and does not interfere with women's regular routines. This device targets the delivery of HAL to the cervix for 5 h, after which it automatically generates illumination with a wavelength of 629 nm for 4.6 h. The differences in PDT applications may have contributed to the variations in treatment outcomes. Although topical photosensitizers such as 5-ALA are more convenient to use and less expensive than intravenous photosensitizers [46], the therapeutic effect is not always consistent. Also, the effectiveness of ALA PDT is significantly influenced by the frequency of treatment sessions. Since then, according to the results of additional authors have attempted PDT utilizing topical Hexyl-ester 5-ALA, an advanced PSZ of 5-ALA, with still poor results of 63 % CR rate [4]. Intravenously ad-ministered photogem showed a positive result of more than 95 % CRR. According to de Freitas et al. cell viability was effectively decreased by photogem, with cytotoxicity being influenced by the light dose [47].

In this study, the median age of patients was also noted, which averaged 32 years and the youngest patient was 18 years old. Similarly, according to Andersson et al. the study's sample of 529 patients had an average age of 34.3 years, 85.6 % of patients were under 45 years of age, and 35.5 % of them were under 30 years of age [48]. Considering that, the age range between 30 and 40 is a peak age of productivity for both the economic and social development of the state, the extensive spread of this disease is a great burden at present and demands appropriate prevention approaches.

This systematic review is consistent with previously conducted systematic reviews and includes the most recent papers. However, it has several limitations, such as the lack of diversity of studies, since the same research team writes most of the included articles, which can limit the

comprehensiveness and generalizability of the review. In addition, the heterogeneity of studies in the systematic review in terms of study design, participant characteristics, interventions, and outcome indicators made it difficult to conduct a meta-analysis. Moreover, the interpretation of the results was limited due to the inclusion of patients with low-severity CIN, who initially have a high degree of spontaneous regression, also a relatively brief follow-up period, and a few numbers of treated patients, which makes it difficult to determine a clearer long-term effectiveness of PDT for the treatment of CIN.

Further research can focus on developing well-designed and organized RCTs that can provide more robust evidence regarding the effectiveness, safety, and long-term outcomes of PDT. Furthermore, exploring the potential for personalized medicine in PDT, such as identifying biomarkers for patient selection and treatment response prediction, can further optimize patient outcomes.

5. Conclusion

Recent research suggests that PDT has demonstrated the most favorable outcomes in the treatment of CIN. However, it should be noted that the efficacy of PDT for HPV-associated CIN treatment may depend on various factors such as the type of PDT agent, the dose and timing of PDT application, the severity and location of the lesions, and the host immune response. Therefore, further studies with larger sample sizes and longer follow-up periods are needed to confirm the findings and optimize the PDT protocols for clinical use.

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CRediT authorship contribution statement

Nasrulla Shanazarov: Writing – original draft, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Gulzada Bariyeva:** Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Andrey Avdeyev:** Writing – original draft, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Rustam Albayev:** Writing – review & editing, Visualization, Conceptualization. **Saule Kisikova:** Writing – review & editing, Conceptualization. **Sergey Zinchenko:** Writing – review & editing, Conceptualization. **Ilfat Galiev:** Writing – review & editing, Conceptualization.

Conflict of interest

The authors have no conflicts of interest to disclose.

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