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Review

5-Aminolevulinic acid-based fluorescence diagnostics of cervical preinvasive changes

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ABSTRACT

The purpose of this article is to review the diagnostic possibilities of 5-aminolevulinic acid (5-ALA)-based fluorescence diagnosis of preinvasive cervical changes.

Reviewed papers were selected from the PubMed database with keywords combining the terms individual cervical neoplasia and fluorescence diagnostics. The regular colposcopy procedure lacks specificity; therefore, new methods are continually sought for superior diagnosis of cervical pathology. 5-ALA-based fluorescence diagnostics is under investigation as an up-to-date diagnostic technique for cervical intraepithelial neoplasia (CIN). This method is grounded on the topical or systemic application of 5-ALA, which induces excess production of the endogenous photosensitizer protoporphyrin IX (PpIX) in tissues where carcinogenesis has begun. The conversion of PpIX to the heme is less efficient in tumors; therefore, higher amounts of PpIX tend to accumulate in premalignant and malignant tissues. Illumination with light of the appropriate wavelength initiates excitation of PpIX fluorescence, which in turn helps to localize PpIX-rich areas and identify potentially malignant tissues. A number of investigations suggest that because of its high selectivity for tumors and low toxicity to healthy tissues, 5-ALA-based diagnosis seems a promising tool for the noninvasive identification of cervical intraepithelial neoplasia.

1. Introduction

About 530,000 new cases of cervical cancer and 275,000 deaths from this disease are reported annually worldwide. The incidence of cervical cancer (CC) varies extensively between countries, with world age-standardized rates (WASR) ranging from <1 to >50 per 100,000 [1]. In the European Union, 34,000 new cases and 16,000 deaths due to cervical cancer are apprised every year. This maiming disease mostly affects younger women between the ages of 35 and 50 [2]. Data from the Lithuanian Cancer Registry proclaims that morbidity from

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cervical cancer reaches up to 19–23 cases per 100,000 (WASR), and mortality is 6–8 per 100,000 (WASR). In 2009, 457 new cases of CC were reported in Lithuania [3], and this is one of the highest rates of morbidity from cervical cancer rate among Baltic countries and also among all the Nordic countries [4].

Cervical intraepithelial neoplasia (CIN) is a precancerous condition of the cervix localized in the squamo-columnar junction. The main factor directly related to CIN development is chronic human papillomavirus (HPV) infection, mainly high-risk types 16 and 18 [5–7]. The classification of CIN ranges from CIN I (mild neoplasia) to CIN III (severe neoplasia). CIN is a condition that gradually leads to cancerous changes; however, those preinvasive changes might require several years [5,7,8]. If CIN is diagnosed at an appropriate time before cervical cancer manifestation, it may be cured and cervical cancer avoided [7–9].

With the aim of early CIN detection, screening programs have been organized worldwide that demonstrate their remarkable influence on cervical cancer morbidity and mortality [1,3,4]. Cervical cancer screening currently consists mostly of cervical cytology, diagnostic colposcopy and HPV testing, depending on national screening policies [2,3]. First and foremost, cytological testing is performed on all women of a particular age. If cytological alterations are found, colposcopy and biopsy of the cervical tissue are indicated. Colposcopy is based on recognizing specific markers in the margins, color, and vascular pattern of an epithelial lesion. This examination is focused on the differences between healthy, premalignant and malignant cervical epithelium and used to guide biopsies to an area or areas as needed [9,10]. There is an imperfect correlation between visual changes in the cervical epithelium and the severity of the intraepithelial neoplasia and cancer [10,11]. Several conditions can also interfere with the accuracy of colposcopic diagnosis (inflammation processes, atrophic changes, and anatomical features limiting the ability to examine a zone of transformation in the cervix) [10,12,13]. The main disadvantages of contemporary CIN detection methods are high false-negative rates with cytology and the low specificity of colposcopy. Conventional colposcopy demands long-term training and achieves no more than 48% specificity even in ''trained hands'' [8,11,12]. The low rates of positive predictive value seen with conventional colposcopy may result in unnecessary treatment, which causes unwarranted surgical procedures for patients and additional burden on cervical cancer screening programs. Various treatment methods that differ mainly in their complication rates and costs have proven satisfactory for CIN treatment [14–17]. The recent standard of care consists of excision, e.g., loop electrosurgical excision procedure (LEEP), cold knife excision of the transformation zone or local destruction by laser or cryotherapy. These procedures are commonly painful during treatment and may cause post-operative bleeding. The major drawback of these excision methods is the destruction of the cervical stroma, which may cause cervical insufficiency that may lead to premature delivery and low-birth-weight babies or, adversely, scar stricture with increased risk of infertility and cesarean section [15–17]. The potential complications of treatment procedures suggest that there is a need for new early diagnostic methods to differentiate CIN and avoid risky surgical procedures. The sensitivity of the method should be high enough to detect CIN in the early stages. However, the procedure should also be quite simple, painless and practical to perform during routine examination or screening programs.

One of the most promising techniques in early diagnostics is the so-called optical biopsy [18–22]. The term ''optical biopsy'' refers to any technique that uses the interaction of light and tissue to provide information about tissue morphology without the need for excision. Premalignant and malignant tissue differs from healthy tissue in its morphology and cell growth rate, which results in altered optical characteristics [13,20,23,24]. Most of the optical methods used in diagnostics are based on different types of spectroscopy such as fluorescence, near infrared, Raman, diffuse reflectance spectroscopy and similar techniques [25–28]; however, the most widely used techniques in the clinical practice are based on fluorescence phenomena [29,30]. The acceptance and suitability of these methods in the clinical arm is determined by the diagnostic effectiveness, simplicity and relatively low cost of the procedure. Moreover, they are noninvasive and can be repeated many times.

Another advantage is that the contrast between healthy and pathological tissue can be enhanced using exogenous fluorescence substances or their precursors [24,31–33]. Fluorescence diagnosis (FD) is also under investigation as an up-to-date diagnostic technique in various gynecological pathologies such as cervical, vulvar intraepithelial neoplasia, endometriosis, breast and ovarian cancer [34–36]. The effort is focused on creating a new noninvasive method to specify the grade of CIN. One of the most promising techniques for this purpose seems to be fluorescence diagnosis based on 5-ALA application [34,37–40]. 5-ALA is an endogenous agent that is metabolized in a chain of biochemical reactions to protoporphyrin IX (PpIX) and is also non-toxic at the levels that naturally occur in the body. PpIX is a precursor of heme in the cells and is also non-toxic in the absence of light of the appropriate wavelength [41–45]. Such a diagnostic method is grounded on the topical or systemic application of 5-ALA, which induces excess production of endogenous photosensitizer PpIX in tissues where carcinogenesis has begun [42,44–46]. This selectivity is partially explained by a lower ferrochelatase activity in tumor cells and a higher tumor level of porphobilinogen deaminase, which are the two key enzymes in regulating the heme pathway [42–44,46,47]. Illumination of the tissues with the appropriate wavelength of light initiates the excitation of PpIX fluorescence, which in turn helps localize PpIX-rich areas and identify potentially cancerous tissues [35,37,42,44].

High selectivity for the tumor and low toxicity to healthy tissues make 5-ALA-based diagnostics a promising tool for the noninvasive identification and staging of cervical intraepithelial neoplasia [48–50]. Moreover, the accumulated porphyrins could also be used for treatment purposes [47,51–53]. Using localized cytotoxic phenomena is the main idea behind photodynamic therapy (PDT), which can be applied as an alternative treatment for cervical intraepithelial neoplasia, avoiding the usual complications with excisional and destructive (laser or cryotherapy) procedures [14,47,54,55]. Various studies have demonstrated a 42%–95% response rate and a 31%–91% cure rate of 5-ALA-based PDT [53]. The therapeutic effect induced by laser light is well-confined to the illuminated area and, together with the short half-life of the generated