Photodynamic therapy - alternative treatment method of oral mucosa inflammatory diseases

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Abstract

Background: Oral mucosa diseases are one of the most common diseases in the world population. And the diseases of periodontal tissues represent the urgent problem of the modern dentistry. According to the various authors their number amounts to 98%. Epidemiological studies show that the disease incidence is increasing in the people from 20 to 35 years old. Many studies have demonstrated the pluricausal nature causing the periodontal diseases. High incidence of periodontal diseases propagation and low efficiency of treatment made it necessary to find the optimal methods of treatment considering the pathogenic mechanisms of periodontal tissues. In this field the method of photodynamic therapy widely used in recent decades generates the special interest. This method of treatment has found popularity for treatment of both oncologic and non-oncologic inflammatory diseases in the dentistry and other fields of medicine.

Method: The phrases "photodynamic therapy" and "periodontal diseases ", were searched for in Google Scholar and Pub Med in May 2017. The results were narrowed to 10 citations after excluding non-English and duplicate reports. Clinical descriptions and outcomes were categorized and analyzed.

Conclusion: By using the photosensitiser “Rada Dent” and the device “Photodin-K” it has become possible to treat the oral mucosa inflammatory disease by non-invasive method. TCM-GMJ May 2017; 2(1):P25-P29

Keywords: Periodontal diseases, Photodynamic therapy, Photosensitiser, Fluorescence, Diode laser.

Introduction

Oral mucosa diseases are one of the most common diseases in the world population. And the diseases of periodontal tissues represent the urgent problem of the modern dentistry. According to the various authors their number amounts to 98%. Epidemiological studies show that the disease incidence is increasing in the people from 20 to 35 years old.

Periodontal disease is pathology of the periodontal membrane. 90% of injuries of periodontal tissues has the inflammatory nature of the periodontal tissues. The most common non-specific, infectious, chronic inflammatory diseases are gingivitis and periodontitis. Usually the pathology begins with gum inflammation, which gradually extends to the subcutaneous area and takes the form, characteristic for periodontitis.

Many studies have demonstrated the pluricausal nature of the periodontal diseases. Some authors believe that the cause is gingival microcirculation disorder, others are talking about the genetic factors, and some authors - about the changes of the immune system. Thus we can divide into the following groups:

- Metabolic and alimentary – the first are nutritional and metabolic disorders
- Endocrine - disorders of hormonal processes during control occurring in the pathologies of thyroid, parathyroid, pancreas and genital glands
- Immune - autoallergy and autoimmunization, humoral and cellular immunity disorders
- Inflammatory-dystrophic, the first among the causative, existence of dental plaque
- Genetic - the existence of genetic factors is revealed in the development of periodontal diseases.

Modern level of knowledge of the etiology and pathogenesis of the periodontal diseases, definitely allows us to define the periodontal microflora as a dominant factor. The bacteria pathogenicity, with regard to the periodontal tissue, has been approved by numerous studies. There are two main theories differently assessing the connection of the inflammatory periodontal diseases with the number and nature of the tooth plaque microbial composition. The author of both theories is W. Loesche:

The theory of the plaque non-specific composition is as follows – parodontium condition depends on the oral hygiene quality. The most common method of treatment -
professional hygiene and the use of antibacterial agents - depends on it.

The theory of the plaque specificity is that only the plaque of the defined composition is pathogenic, and its pathogenicity depends on the increasing or even the existence of the number of those microorganisms defined in the plaque composition. It has been proved that the development of the periodontal tissues inflammatory diseases is most often associated with the persistence of the microflora representatives, such as Prevotella intermedia, Porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans, F. Nucleatum.

Treatment methods of inflammatory periodontal diseases are various:
- Etiotropic therapy, aimed at eliminating of the causative reasons
- Pathogenic therapy, aimed at the pathogenic processes circle
- Sanogenetic therapy, enhancing of protective - adaptive mechanism
- Restorative therapy

In modern reality, the special emphasis is given to the use of products of plant origin that is conditioned by expressed therapeutic effect, non-toxicity, cumulative effect of these products, allowing the patients to use them without any risk for a long period of time.

Despite the successes achieved, the improvement of the effectiveness of the treatment of inflammatory periodontal diseases still remains a topical issue.

Photodynamic Therapy

High frequency of periodontal diseases propagation and low efficiency of treatment made it necessary to find the optimal means of treatment considering the periodontal tissues pathogenic mechanisms.

In this field the method of photodynamic therapy widely used in recent decades generates the special interest. This method of treatment has found popularity for treatment of both oncologic and non-oncologic inflammatory diseases in dentistry and other fields of medicine.

The basis of the photodynamic therapy is a special chemical product – photosensitiser which is locally activated by the electro-magnetic radiation. Thus the photochemical reaction impacting the tissue is in progress.

Radiation exposure of the tissue may be implemented both in the oxygen and oxygen-free medium.

The photodynamic therapy mechanism is represented as follows: photosensitiser's molecule absorbing the ray quantum is transferred into the excited triplet state and enters into the photochemical reaction of the type 2.

In case of the reaction of the type 1, the interaction occurs directly with the biological substrate resulting in the formation of free radicals.

During the reaction of the type 2 the interaction occurs between excited photosensitiser and open molecular oxygen.

Oxygen-dependent interaction between the substance and the ray (so called photodynamic therapy of the type 2) was discovered by O.Raab in 1898. He was a student of the Department of Pharmacology at Munich University (Director, Professor - H.FON Tappeiner). The discovery was made on the elementary oncocellular product (Paramécium) 41. He noticed that the Paramecium actively moved in the die solution – "acridine red" both in the darkness and in the incubation daylight without die. The Paramecium died in the combination of the "acridine red" and the daylight. The main factor of the injury in their mechanism of their destruction was the dye fluorescence as a result of the ray exposure. O.Raab supposed that the substrates exposed by fluorescent, for example, acridine dye, transform the ray energy into the "active chemical energy" leading to the Paramécium destruction. This natural dye was named “photosensitiser” - (H.Tappeiner,1904).

Initially this term was used in all processes where the photosensitiser, living tissue (cell) and the irradiation procedure were used in.

Later in 1941 H.F.Blum began to use this term (photosensitiser, photodynamic therapy) only for description of the processes where only the active oxygen participated in the tissue dissolution mechanism in case of ray excitation 43.

Since then, this processes includes those in which there is no primary injure of the tissue, and the tissue dies not immediately but after the certain biochemical and immunological processes. As a result of such photomodified action the cells with antigen-presentable action and tumor-specific memory are activated in the photomodified cell markers. As a result the immune response is evolving. This is accompanied by the active anti-tumor immune response. Including the carcinolytic one. These will be detected by the above immune system away from the primary lesion (where the exposure of photosensitiser, oxygen and ray occurred for the first) 44.

Photodynamic therapy soon found its place in oncology. It turned out to be useful for treating of the oncológic diseases of the organs such as otorhinolaryngologic organs, digestive tract, stomach, skin tumors and the oral cavity organs, the thyroid gland pathologies.

Medicines used during the photodynamic therapy - photosensitiser is a natural or artificially synthesized substance causing the sensibilization of the biological tissues, i.e. increase its sensitivity to the radiation exposure.

The predecessor of the modern photodynamic therapy may be considered the tests of the ancient Greeks and Egyptians to use the ray absorber medicines during skin diseases. We know from the ancient historical sources that the botanical medicines causing the skin photoreaction were used in Egypt 6 thousand years ago. These medicines were used for treatment of depigmentic areas (vitiligo). The natural photosensitiser (psoralen) contained in the composition of the plants, such as Pasternak, parsley, were used, and they were activated by the sun ray.

After application by the powder of the above plants the depigmentic area was exposed by light sun ray, the suntan-type pigmented spots appeared on the areas.
In 1550 BC the potomedicine procedures were described in the “eberal” papyrus and Indian holy book “Athara Veda”\(^{50,51}\).

The intensive researches of psoralen were held, the active substances were separated and their chemical analyses were conducted in the previous millennium in Egypt. Soon after the main and most important compound - 8-methoxypsoralen was used for the treatment of psoriasis. In this case the photosensitivity and photo-chemical reaction was proceeded by using psoralen without using oxygen. (photodynamic type 1)\(^{52}\).

The first data on the photosensitiser of tetrapyrroles group – haematoporphyrin was made by W.H. Hausmann in 1908. He found that haematoporphyrin is an active sensitisir for Paramecium and the erythrocytes.

For the first time the sensational experiment of the effect of haematoporphyrin on the human body was made on himself by F. Mayer on October 14, 1912. He administered intravenously 0.2 g of haematoporphyrin and presented the sun ray photosensitivity in the form of hyperemia and hyperpigmentation which lasted for 2 months. Further researched showed that the systemic use of haematoporphyrin causes an intensive photosensitivity of different tissues\(^{53}\).

The importance of fluorescence diagnostics of the neoplastic cells conducted by using of haematoporphyrin was emphasized by A. Poliard in 1924\(^{54}\). He said that the red fluorescence caused by ultraviolet ray, in rats by the experimental sarcoma, is conditioned by the accumulation of endogenous haematoporphyrin, as a result of secondary infection with haematological bacteria.

For that moment it was important for the development of the modern photodynamic therapy to create an improved photosensitisir, an improved version of producible haematoporphyrin which turned out to be twice more toxic, and having twice higher photodynamic effect than the primary product. Haematoporphyrin itself is a mixture of porphyrine and inert impurities.

As it became known, later the producible haematoporphyrin is a porphyrins mixture which has still not active or low photosensitive activity. Improved mixture was taken by Schwartz-Lipson (1961) method based on the Dougherty’s (1979) papers. His idea was as follows: the optimum oligomerization progress was improved by the alkaline medium improvements, and its infusion was additionally used as an agent\(^{55}\).

In September 1981 R. Bonnett first observed that after alkaline processing haematoporphyrin acetate had an oligomeric nature and contained 3 types of binding: (C-C, C-Ο-C and C(Ο)Ο-C)\(^{56}\). It was the compound that determined the biological activity of producible haematoporphyrin. It may be separated from other components through various chromatographic methods. The product containing at least 80% of these active fractions is known as “Photophrin II”\(^{57}\).

The Canadian product “Photophrin-II” is considered to be the most common and effective photosensitisir. However, the experimental studies showed that it had developed deceleration in skin during the minimum concentra-

tion which requires the certain radiation doze. Special attention should be paid to the light ray (the sunray) contact on the skin for 4-6 weeks, in order to avoid the skin reactions with the radiation burn effect\(^{58,59}\).

Further, it were developed the various analogs such as of the Russian origin – “Photophrin I” - the analog of “Photophrin II” which later was named as “Photogem”\(^{60}\).

In the modern reality the list of photosensitisers is long: “Photosens”, “Alasens”, “Photoditazini”, „Radahlorin“ (Russia); “Foscan” (Germany); “Mettix” (Switzerland); „Purlthyn“ (USA) and others.

Modern photosensitisers have a number of optimality criteria: Low photoxicity; Selective accumulation in tumor-origin issues in respect to healthy tissues and fast expulsion from the body; Indispensable composition (in some works it is emphasized that the photosensitive component should be the pure substance); High quantum expulsion from the triplet state and the energy of at least 94 kJ/mol (excitation energy is needed to generate the singlet oxygen); Visible absorption of red light of visible spectrum because this ray penetrates the tissue the most well.

Such an optimal and clinically usable photosensitisir is „Radahlorin“, which is of Russian origin known abroad as “Bremachlorin”. It was developed by Reshetnikov in 1995-2006.

We decided on it due to its special features: Water-soluble; Indispensable composition; (80-90%) Chlorine e6, 2-15% Purpurin 5 and 5-20% Chlorine p6); Low-toxic; Plant origin; Upon radiation has the ability to produce the large volume of singlet oxygen, simultaneously for the diagnostics; Quickly accumulated in the pathologic focus, kept for a long time (24 hours), herewith quickly excreted from the healthy tissues and generally from the body; Accumulated only in the pathologic focus at the expense of high selectivity; High clinical effectiveness.

Considering the above mentioned advantage, it was developed the modification of “Rada Chlorine” – “Rada Dent” that is for dental purposes. Its use during the oral mucosa inflammatory diseases makes more effective the treatment with the photodynamic therapy\(^{61}\).

**Ray source for photodynamic therapy**

Back in 1916 Einstein predicted the existence of the event of forced radiation, this is the physical basis for the work of all lasers. The first studies relating to the use of laser were conducted in the sixties of the last century. As well the first medical laser equipment appeared in the sixties. In 1965 the first surgical manipulation with medical laser was conducted in the Soviet Union. And in 2015 the medical laser turned 55.

Laser with argon paint has been used in the world practice for a long time, further the metal steam was used for the base. The dyes in these types of lasers were used for the wavelength reorder. The above lasers were large, they were needed three-phase high current, and in addition it was expensive. They were replaced by the lasers with the
gold steam generating the ray with the wavelength of 628 nm. This type of laser device turned out to be usable for photodynamic therapy. Laser device according to the wavelength may be used for work both on soft and hard tissue.

4 Basic types of laser of different wavelength are used in dentistry:
- Diode laser - 630-970 nm
- CO2 laser 1060 nm
- ND YAG laser – 1064 nm
- ER YAG laser – 2960 nm

New stage of development of photodynamic therapy turned out to be compact, affordable laser diode devices. Each of them generates the same wavelength, therefore it will be selected considering its absorption peak with the photosensitiser. For a long time nobody could create the diode laser with the required power for generation of the red ray of wavelength of 630 nm. This wavelength is acceptable for most photosensitiser.

Similar lasers have been created in the USA. Today it already has a Russian analogue – the device under the brand “Polironik” for photodynamic therapy – “Photodin-K” with wavelength of 660 nm.

It should be emphasized that the photodynamic therapy became clinically available by developing, approbation and implementing of the second generation photosensitisers. The second generation photosensitisers differ from the traditionally used photosensitisers. They have a high therapeutic efficacy, the ability of better selection, more rapid pharmacokinetics. In addition, it is consistent with the whole range of wavelengths generated by the diode lasers; they appeared to be more effective, compact, economic. It should be also noted the ease and comfort of their practical use compared to the lasers of older generation which had the dyes and the ionic charge.

Thus, by using the photosensitiser “Rada Dent” and the device “Photodin-K” it has become possible to treat the oral mucosa inflammatory disease by non-invasive method.

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