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Study of ALA and small dosage of HPD photodynamic therapy (HPD-PDT) in treatment of skin cancer.

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Abstract

Objective: To investigate clinical effect of ALA and small dosage of HPD-PDT in treatment of patients with skin cancer.

Methods: From June 2014 to April 2017, 62 cases of malignant skin tumor patients treated in our hospital were selected as the objects and randomly divided into study group (31 cases) and control group (31 cases), respectively treated by ALA and small dosage of HPD-PDT and conventional HPD-PDT. The clinical effective rate and recurrence incidence in the two groups were compared to explore therapeutic effect of ALA and small dosage of HPD-PDT on skin cancers of different types.

Results: The effective rate of the study group (100%) was significantly higher than that of the control group (87.09%) while the recurrence rate of the study group (3.23%) was significantly lower than that of the control group (19.35%) of statistical significance, P<0.05. Besides, the study group has more significant effects in treatment of skin cancers like adnexal tumor, basal cell carcinoma, malignant melanoma and squamous cell carcinoma.

Conclusion: The clinical effect of ALA and small dosage of HPD-PDT has significant curative effects in the treatment of various skin tumors.

Keywords: Aminolevulinic acid (ALA), Hematoporphyrin derivative (FPD), Photodynamic therapy (PDT), Skin cancer.

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Introduction

The skin, lying on the outermost layer of human body, is the largest organ of people [1]. It is both sensory and effector of nervous system. Mechanical and chemical stimulations sensed by the human body like cold, heat, pain and mood changes will cause reflection of cutaneous vascular in the form of contraction and relaxation, muscle contraction, secretion of sweat and change of skin capillary permeability [2-5]. Skin tumor is one of the most common diseases in clinical trials and it will seriously affect the health of the patients when the tumor progresses to advanced stage [6-8]. ALA (5-Aminolevulinic Acid) is the main raw material for the synthesis of heme and in this process, with enzyme activation ALA can produce a more efficient photosensitizer named PPIX (Protoporphyrin), which combines with FE to generate necessary heme that human body needs under the action and influence of ferrous chelates of enzyme. Most of the ferrous chelates present in the tumor have low activity and therefore the high content or overproduction of ALA would hinder the effective conversion of PPIX, making most of PPIX remain inside the tumors of the patients. In addition, the PPIX content in normal human tissues was significantly lower than that in the site of tumor. Thus, after ALA input *in vitro*, ALA is converted into PPIX photosensitizer in the tumor, setting a good foundation for PDT (Photodynamic Therapy) treatment and effectively reducing the side effects caused by skin treatment. ALA-PDT therapy has been the research focus in the field of PDT since 90s. To improve the treatment and prognosis of patients with skin malignant tumors, the application of ALA and small dosage of HPD (Hematoporphyrin derivative)-PDT was specially carried out in our hospital with remarkable effects reported as below.

Materials and Methods

Materials

From June 2014 to April 2017, 62 patients with malignant skin tumors treated in our hospital were selected as the study objects and they were diagnosed as malignant skin tumors by pathological diagnosis. The selected cases were randomly divided into study group (31 cases) and control group (31 cases) in which the study group included 16 males and 15 females at the age of 52-83 and with the average age of 65.2 ± 3.4, among them there were 5 cases of eccrine carcinoma, 12 cases of basal cell carcinoma, 3 cases of malignant melanoma and 11 cases of squamous cell carcinoma; while the control group consisted of 14 males and 17 females at the age of 53-84

and with the average age of 65.9 ± 3.5, among them there were 7 cases of eccrine carcinoma, 10 cases of basal cell carcinoma, 4 cases of malignant melanoma and 10 cases of squamous cell carcinoma. There was no significant difference in the general information between the two groups (P>0.05), making it proper to conduct the experiment.

Treatment methods

The patients in the control group received conventional therapy. The patients in the study group underwent ALA and small dosage of HPD-PDT. After the complement of routine disinfection and anesthesia, specimens of the affected areas were taken to be examined. Gasification and laser therapy were performed for treatment of advanced tumor followed by routine test of urine and blood as well as function of heart, lung, liver and kidney. HPD skin test was conducted and the patients with negative result were treated by intravenous injection of 250 ml saline and HPD (1.5 mg/kg) mixture, and 48 h later received photodynamic therapy and avoided light irradiation during this period. ALA with the concentration of 8% was used for external application followed by being wrapped with preservative film and laser photodynamic therapy was performed after 4 h. After treatment, a follow-up of 2 y was conducted to investigate the recurrence of the tumor.

Clinical observation index

The criteria for evaluating the efficacy of tumor treatment are as follows [9]: Cure (CR): the clinical symptoms completely disappeared and the pathological findings showed no lesions; Markedly effective (PR): tumor volume decreased by at least 50%~90%; Effective (MR): tumor volume decreased by less than 50%; Ineffective (NR): tumor volume decreased by less than 20% or the condition went worse. The total effective rate of clinical treatment=(the rate of cure+markedly effective rate +effective rate)/the total number of cases × 100%.

The recurrence rate was compared between the two groups.

Statistical analysis

Count data were expressed by "percent" (n, %). Chi square test was carried out on SPSS 19.0 software for statistical analysis. p<0.05 suggested that the difference had statistical significance.

Results

With different treatment methods, the effective rate of the study group was 100% and the recurrence rate after treatment was 3.23%, significantly different from the corresponding data (respectively 87.09% and 19.35%) of the control group of statistical significance (P<0.05). The study group showed better clinical treatment effects (Table 1).

Table 1. Comparison of effectiveness and recurrence rate in the two groups.

Group	CR	PR	MR	NR	Total effective rate	Recurrence rate
Study	28	3	0	0	31	1
Control	17	8	2	4	27	6
χ^2					4.276	4.026
P					0.039	0.045

31 patients in the study group included 5 cases of eccrine carcinoma, 12 cases of basal cell carcinoma, 3 cases of malignant melanoma and 11 cases of squamous cell carcinoma. With the treatment of ALA and small dosage of HPD-PDT, the clinical symptoms of various skin tumors were significantly improved (Table 2).

Table 2. Effect of ALA and small dosage of HPD-PDT on skin tumors of various types.

Tumor type	CR	PR	MR	NR	Total effective rate
Eccrine carcinoma	4	1	0	0	100.00
Basal cell carcinoma	9	2	1	0	100.00
Malignant melanoma	3	0	0	0	100.00
Squamous cell carcinoma	10	1	0	0	100.00
Sum	26	4	1	0	100.00

Discussion

Relevant research results show that in the treatment of skin tumor diseases, compared with single application of ALA or HPD, the combination of the two enables to not only make up for each other's deficiencies but also reduce the dose of drug use to further develop drug effects [10,11]. In the previous treatment, the dose of HPD would be frequently set as 5 mg/kg and the concentration of ALA was often 20%. In this study, however, we lowered the ALA concentration and reduced the dose of HPD. This kind of combined application can shorten light avoidance time that is necessary for the treatment and improve treatment compliance and life quality of the patients [12].

ALA is featured by hydrophilic nature and zwitterion ions, thus making it hard to penetrate cell membrane. But lipid derivatives of ALA have stronger lipid solubility and stronger penetrating power when entering and leaving cells. Moreover, compared with the healthy, patients with malignant skin tumors are more defective in the barrier of skin penetration, which can improve the effect of local application of esterified ALA [13-15]. ALA is one of new photosensitizers and its application gives rise to minimal side effects, which contributes to its biggest characteristics and advantage. When ALA rests on the human body for about 3 h, the PpIX content of the patients reaches the highest level, and then decreases gradually after 6 h and until after the 24 h, the test results show almost no PpIX in the body of the patients. Besides, the routine examination of patient's blood and urine as well as liver and kidney function showed no abnormality, revealing its high security [16-18]. Considering allergy reactions like shock, palpitations and chest tightness in application of HPD, skin sensitivity test should be conducted before the trial. Patients with no allergic reaction can be treated in this way while those with allergic reaction are required to free from the use of the drug to reduce and avoid severe allergic reactions [19]. The results of this study showed that the efficacy rate of combined treatment of ALA and small dosage of HPD-PDT in clinical practices was 100% and the recurrence rate was 3.23% with more obvious and ideal treatment effects compared with the control group of statistical significance, $P<0.05$. This kind of therapy is highly effective, like result of the research by Wang et al. [20].

In addition, Photodynamic Therapy (PDT), one of effective methods for the treatment of skin diseases, has high lethality to tumor tissues. It also belongs to minimally invasive techniques and patients demanding of good skin appearance can choose this therapy. Besides, most of the patients have better tolerance to this treatment, so elder patients or patients with weak constitution can also choose this kind of treatment to reduce the burden on the body.

But the number of cases selected in this study is moderately small and the skin cancer types of the patients are few, making it difficult to guarantee this kind of treatment has the same effects on all skin cancers. Therefore, research on this kind of treatment method will continue to be carried out with the enlargement of scale, rising number of cases and tumor types to achieve more rigorous and accurate research results, thus providing good treatment options for patients with skin tumors.

Conclusion

ALA and small dosage of HPD-PDT therapy has good therapeutic effect and prognosis of high security, worth being popularized and applied in clinical treatment of skin tumors.

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