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ORIGINAL RESEARCH ARTICLE

Effect of cryotherapy and ALA-PDT therapy on skin cancer

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***Abstract*: Objective:** to study the effect of cryotherapy and ALA-PDT therapy on skin cancer. **Methods:** this study selected 60 patients with skin cancer admitted to Ankang People's Hospital of Shaanxi Province from January 2014 to December 2019. According to different treatment methods, 30 patients treated with ALA-PDT were included in the control group, while 30 patients treated with cryotherapy combined with ALA-PDT were included in the observation group. The total effective rate, pain score, surgical trauma area, incidence of adverse reactions and total satisfaction rate of appearance were compared between the two groups. **Results:** the treatment efficiency of the observation group was 96.7%, which was higher than that of the control group (73.3%), with a statistically significant difference ($P < 0.05$). The pain score in the observation group was (4.12 ± 1.03), higher than that of the control group (3.45 ± 0.86), and the surgical trauma area was (1.26 ± 0.04) cm^2, lower than that of the control group (1.39 ± 0.05) cm2, with a statistically significant difference ($P < 0.05$). The difference was statistically significant (all $P < 0.05$). There was no significant difference in the incidence of adverse reactions between the two groups ($P > 0.05$). Besides, the total satisfaction rate of the observation group was 93.3%, which was higher than that of the control group (66.7%), and the difference was statistically significant ($P < 0.05$). **Conclusion:** Cryotherapy combined with ALA-PDT therapy are clinically effective in the treatment of skin cancer, with less invasive surgical areas and higher patient satisfaction with appearance. However, the pain score is relatively higher. Therefore, the appropriate treatment can be clinically considered in a comprehensive manner.

Keywords: cryotherapy; ALA-PDT therapy; cutaneous tumor; effect

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Introduction

Skin cancer, a common malignant tumor in clinic, often occurs on the head, back of the hands and vulva, and is commonly seen in people over 60 years of age[1]. The incidence of skin cancer is related to heredity, ultraviolet, smoking and virus infections, among which the occurrence of skin cancer is 3–4 times higher in people with long-term ultraviolet exposure and smoking than in the general population[2]. With the progress of skin cancer, early lymph node metastasis and blood metastasis are prone to occur, and the prognosis is poor. The 5-year survival rate is less than 35%, which seriously affects the image and health of patients[3]. For the treatment of skin cancer, surgery, cryotherapy, laser and external medicine are mainly used. ALA-PDT is a non-invasive treatment method, which is targeted and not limited by the location and size of the lesion. It has been widely used in clinical practice[4]. Cryotherapy provides irreversible damage to the tumor, completely destroying the tumor tissue and thus achieving complete elimination of the tumor[5]. This study investigates the clinical effects

of cryotherapy in combination with ALA-PDT therapy in patients with skin cancer.

Materials and methods

General materials

This study selected 60 patients with skin cancer admitted to Ankang People's Hospital of Shaanxi Province from January 2014 to December 2019. According to different treatment methods, 30 patients treated with ALA-PDT were included in the control group, while 30 patients treated with cryotherapy combined with ALA-PDT were included in the observation group. Inclusion criteria: 1) All patients were diagnosed as skin cancer by pathological examination. 2) None of the patients had distant metastases. 3) Patients received no treatment prior to joining the group. 4) Patients and their families signed informed consent. 5) The study was approved by the Hospital Medical Ethics Committee. Exclusion criteria: 1) Patients with other malignant tumors. 2) Patients with photosensitive diseases or allergy to photosensitizers. 3) Patients with mental disorders. 4) Patients in pregnancy and lactation. In the control group, there were 14 males and 16 females. Their age ranges from 45–76 (61.25 ± 3.41) years, and the skin lesion area was 0.8–5.3 (3.12 ± 0.85) cm^2. Site: head and face 20 cases, limbs 8 cases, trunk 2 cases. Pathological type: basal cell carcinoma 18 cases, squamous cell carcinoma 12 cases. In the observation group, there are 16 males and 14 females. Their age ranges from 45–76 (60.85 ± 3.13) years, and the skin lesion area was 0.8–5.3 (3.25 ± 0.88) cm^2. Site: head and face 19 cases, limbs 9 cases, and trunk 2 cases. Pathological type: basal cell carcinoma 17 cases, and squamous cell carcinoma 13 cases. There was no significant difference in the general data between the two groups ($P > 0.05$), indicating comparability.

Therapies

(1) The patients in the control group were treated with ALA-PDT therapy, and the skin lesions of the patients were disinfected. If the scab was soaked in normal saline for several minutes, the scab, necrotic tissue and exudation were removed. 118 mg of 5-aminolevulinic acid powder was configured into 20% liquid with injection water, and then injected into the special cotton patch, and the cotton patch was fully infiltrated. The application range was more than 10 mm at the edge of the lesion visible to the naked eye. The external polyethylene thin film was used to seal the package, and the gauze was covered and fixed with plastic cloth. Then, the color plastic film was deepened to avoid light. After the patient was sealed in dark for 3 hours, the envelope was removed, the secretion and residual pharmaceutical solution were removed, and the infrared ray was used for irradiation. The infrared probe was 5–10 cm away from the lesion, and the power was 60–80 mW/cm^2. The irradiation lasted for 30 minutes. Multiple light spots could be used for patients with multiple lesions or large areas. (2) The patients in the observation group were treated with cryotherapy combined with ALA-PDT, and routine disinfection was performed on the skin lesions of the patients. The skin lesions were repeatedly frozen and thawed by liquid nitrogen cotton swab until 0.2 cm of micro-red on the edge of the skin lesions. Then, ALA-PDT was immediately used, and the specific operation was the same as that of the control group. Both groups were treated 3–6 times, once every two weeks.

Observation index

1) The treatment efficacy of the two groups was compared. The assessment criterion included: complete remission: complete disappearance of lesions, pigmentation only, no pathological changes on histopathological examination; partial remission: lesions reduced by 20%–99%; invalid: lesions reduced by <50%; effective rate = (complete remission + partial remission)/total number of cases × 100%. 2) The pain scores, surgical wound area and incidence of adverse reactions were compared between the two groups. Pain scores were evaluated using a visual analogue scale, with a score of 0 indicating no pain and 10 indicating very painful. Adverse reactions include local erosion, local edema, exudation and pigmentation. 3) Comparing the appearance satisfaction level of the patients in the two groups, which was divided into three levels of being satisfactory, fair and unsatisfactory. Total satisfaction rate = (satisfacotry + fair) total number of cases × 100%.

Statistical method

SPSS 22.0 statistical software was used for data processing. The measurement data were expressed as mean ± standard deviation ($\bar{x} \pm s$), and t test was performed for comparison between groups. Count data were expressed as %. x^2 test was performed the comparison between groups, and $P < 0.05$ indicated that the difference was statistically significant.

Results

1) Comparison of treatment efficiency between the two groups: the efficiency of the observation group was

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96.7%, which was higher than that of the control group (73.3%), and the difference was statistically significant ($P < 0.05$, as shown in **Table 1**).

2) Comparison of pain score, surgical trauma area and incidence of adverse reactions between the two groups: the pain score of the observation group was higher than that of the control group, and the surgical trauma area was lower than that of the control group, with statistically significant differences (all $P < 0.05$, **Table 2**). The difference in the incidence of adverse reactions between the two groups was not statistically significant ($P > 0.05$).

3) Comparison of appearance satisfaction between two groups: the overall satisfaction rate of the observation group was 93.3%, which was higher than 66.7% of the control group, and the difference was statistically significant ($P < 0.05$, **Table 3**).

Table 1. Comparison of treatment efficiency between the two groups [case (%)]

Group	Case(s)	Complete remission	Partial remission	Invalid	Effective rate
Observation group	30	12 (40.0)	10 (33.3)	8 (26.7)	22 (73.3)
Control group	30	20 (66.7)	9 (30.0)	1 (3.3)	29 (96.7)
x^2					6.41
P					0.03

Table 2. Comparison of pain score, surgical trauma area and incidence of adverse reactions between the two groups ($\bar{x} \pm s$)

Group	Case(s)	Pain score	Surgical trauma area	Incidence of adverse reactions
Control group	30	3.45 ± 0.86	1.39 ± 0.05	9 (30.0)
Observation group	30	4.12 ± 1.03	1.26 ± 0.04	6 (20.0)
t/x^2		4.74	5.57	0.80
P		<0.05	<0.05	0.37

Table 3. Comparison of appearance satisfaction between two groups [case (%)]

Group	Case(s)	Satisfactory	Fair	Unsatisfactory	Total satisfaction rate
Control group	30	12 (40.0)	8 (26.7)	10 (33.3)	20 (66.7)
Observation group	30	22 (73.3)	6 (20.0)	2 (6.7)	28 (93.3)
x^2					6.67
P					0.03

Discussion

At present, surgery is still the first choice for skin cancer treatment, which can significantly improve the 5-year survival rate of patients. But for patients with special location and large tumors, there are disadvantages such as greater surgical trauma, incomplete treatment and higher recurrence rate, which are not conducive to the prognosis of patients[6]. In this case, ALA-PDT therapy can be used as a preferred treatment, but the penetration of drugs and the limitation of light depth in this method make the treatment ineffective and require combined treatment to achieve satisfactory results[7]. Therefore, in this study, cryotherapy combined with ALA-PDT therapy were applied to patients with skin cancer to provide the basis for clinical treatment. The results of this study showed that the pain score of the observation group was higher than that of the control group, and the area of surgical trauma was lower than that of the control group. There was no difference in the incidence of adverse reactions between the two groups. The total satisfaction rate of the appearance of the patients in the observation group was higher than that of the control group, indicating that the application of cryotherapy and ALA-PDT therapy in skin cancer could improve the clinical therapeutic effect, without increasing the incidence of adverse reactions, and the patients had high satisfaction with the appearance. This is due to the fact that 5-aminolevulinic acid in ALA-PDT therapy can specifically bind to the sulfhydryl group on the surface of tumor cell membrane, which provides the basis for laser irradiation. Laser irradiation can promote the release of genetic materials in tumor cells and induce apoptosis of tumor cells[8]. The combination of the two can promote the absorption of necrotic tumor tissue, provide space for the absorption of basement membrane dermal cells, and provide attachment surface for the growth of new granulation tissue, thereby promoting wound healing and im-

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proving appearance[9]. Cryo-technology can directly destroy tumor cells, causing them to dehydrate and become necrotic. It can also promote the body to produce systemic specific cellular immunity and improve anti-tumor immunity[10]. In addition, cryotherapy can increase the $CD4^+/CD8^+$ of patients with skin cancer and inhibit the proliferation of tumor cells[11]. The combination of ALA-PDT therapy and cryotherapy not only has the advantages of ALA-PDT therapy for small tissue damage, good aesthetics and small adverse reactions, but also has the advantages of rapid cryotherapy, which effectively improves the clinical treatment effect of patients. In this study, the pain score of the observation group was significantly higher than that of the control group, indicating that the pain of patients with combined cryotherapy was obvious. This was due to the cumulative effect of the duration and extent of pain when both methods were applied simultaneously[12]. This study also had some shortcomings, with a small number of cases included and no long-term follow-up, which will be carried out in subsequent studies. In summary, cryotherapy and ALA-PDT therapy for skin cancer are clinically more effective, with less invasive surgical areas and higher patient satisfaction with appearance, but higher pain scores. The appropriate treatment method can be comprehensively considered in clinic.

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