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Therapeutic Doses of High Intensity Focused Ultrasound in the Treatment of Non-Neoplastic Epithelial Disorders of the Vulva

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Abstract

Objective: Non-neoplastic epithelial disorders of the vulva (NNEDV) are common causes of refractory vulvar pruritus. Focused ultrasound is a noninvasive physical therapy, with higher therapeutic effects and cure rates than local glucocorticoid. Up to now, there have been no studies on the therapeutic doses of vulvar focused ultrasound, and reasonable time and doses are important in standardizing procedures, improving therapeutic effects and reducing complications. Hence, we aimed to explore the long-term therapeutic effects, reasonable treatment time and dose ranges. Methods: All patients who were diagnosed with NNEDV and underwent focused ultrasound treatment in Obstetrics and Gynecology Hospital of Fudan University from 2007 to 2016 were included. Treatment areas, durations, doses, efficacy and other related data were collected.

Results: The effective rates of vulvar pruritus, skin elasticity, color and improvement in the quality of sexual life were 96%, 88%, 78% and 69%, and the recurrence rate was 24%. The effective and the best therapeutic doses per unit area were 41 ± 22 J/cm2, 27 ± 12 J/cm2, respectively. Conclusion: Focused ultrasound is an effective therapy of NNEDV. The quantitative therapeutic doses based on lesion areas may help clinicians decide standardized treatment programs.

Keywords: high intensity focused ultrasound; Non-neoplastic epithelial disorders of the vulva

Introduction

In non-neoplastic epithelial disorders of the vulva (NNEDV), lichen sclerosis and squamous epithelial hyperplasia are the two most common causes of refractory vulvar pruritus. In histopathology, squamous epithelia are thinner in the former and thicker in the latter; dermal fibrosis and lymphocyte infiltration can exist in both. Focused ultrasound is a noninvasive physical therapy. High intensity focused ultrasound (HIFU) can be effectively transmitted to the lesions in the skin. As the ultrasound energy passes through tissue it is attenuated exponentially and the attenuated energy is mostly converted into heat in the tissue, resulting in coagulation necrosis, tissue reconstruction and improvement of blood circulation. A number of studies have reported the high therapeutic effects and cure rates of HIFU [1-4]. Since HIFU can effectively improve the skin elasticity, it has been used in skin lifting and tightening in dermatology [5-7]. However, as far as treatment methods are concerned, previous reports only suggested that the treatment time was based on the areas and degrees of lesions (ranging from 8-60 minutes) and treatment should stop when local skin edema occurred [3,8]. Therefore, the degrees of treatment were decided according to clinician experience, which could vary greatly and cause inadequate or excessive treatment, such as scald, ulcers and so on. The quantitative time and doses of are of great significance for standardizing procedures, improving therapeutic effects and reducing complications. Up to date, there have been no studies on therapeutic doses in the field of vulvar focused ultrasound treatment. Hence, we conducted a retrospective study of long-term efficacies, reasonable treatment dose range of HIFU in NNEDV patients.

Materials and Methods

Patients

Patients who were diagnosed with squamous epithelial hyperplasia or lichen sclerosus and underwent HIFU

treatment in our hospital with complete follow-up data were included from January 1, 2006 to December 31, 2017. All patients were diagnosed with NNEDV by multiple punch biopsies before treatment. Colposcopically directed biopsy were performed by the colposcopists in the Cervical Disease Center of the Obstetrics and Gynecology Hospital of Fudan University (OGHFU). All histological specimens were interpreted by an experienced pathologist and then verified by another senior pathologist. Approval was obtained from institutional review board of OGHFU before the data extraction was performed, and all patients gave consent to research.

Treatment Methods

Patients were treated in intermenstruum when the biopsy wound had healed. Routine vaginal discharge examinations were completed. Patients were placed with lithotomy position. After routine disinfection and draping, local anesthesia with 2% lidocaine were performed. After 2 minutes (min), patients began to be treated with a model CZF (Chongqing HIFU Technology, Chongqing, China). The treatment parameters included power 3.5~4W, frequency 10 MHz, pulse 1000Hz. Ultrasound couplant were applied on the surface of lesions and the probe was in close contact with the skin above the lesion. A consecutive scanning at a speed of 3~5mm/s was performed on the entire lesion area and 5 mm beyond the edge of the lesion. The scanning generally lasted for a period of 1~5 min until the treatment area showed mild congestion, edema, and pink appearance. All treatment areas were disinfected again with iodophor in the end of treatment. All information including treatment area, time, doses and parameters were recorded in special HIFU notebook.

Follow-Ups and Evaluation of Therapeutic Effects

Patients were followed up regularly after treatment to observe the efficacy, side effects of the treatment, and recurrence of the lesion. Outpatient check-ups were at 1 month, 3 months, 6 months and then annually after the treatment. In follow-ups, relative questions were asked about pruritus and sexual satisfaction. Gynecological examinations were performed to identify changes in lesion areas, skin color and elasticity. No, mild, moderate and severe pruritus scored 0, 1, 2, 3, respectively. Based on changes in the degrees of symptoms severity and signs before and after treatment, efficacy was assessed using the following criteria [9].

Curative: symptoms such as vulvar pruritus disappeared, skin color and elasticity of the diseased area became normal;

Effective: symptoms decreased, skin color and elasticity partially recovered;

Ineffective: symptoms such as vulva pruritus continued and signs of local skin did not change, or such signs and symptoms recurred within 6 months after treatment;

Recurrent: symptoms such as vulvar pruritus recurred, skin depigmentation and elasticity decreased 6 months after treatment. The total effective rate was the ratio of curative and effective patients to total patients.

Statistical Analysis

An independent t test was used for statistical analysis and conducted using SPSS 16.0 (SPSS Inc., Chicago, Illinois, USA). A P value < 0.05 was considered statistically significant.

Table 1: Clinical features of NNEDV patients in HIFU treatment.

Diagnosis	No. of patients
lichen sclerosis	39 (42%)
lichen simplex chronicus	54 (58%)
No. of treatment	
1	57 (61%)
2	32 (35%)
3	3 (3%)
4	1 (1%)
Total	93 (100%)
Average duration (range) (s)	113±38 (41-320)
Average doses (range) (J)	394±117 (126-960）

Table 2: Therapeutic effects after HIFU treatment.

Symptoms and signs	Ineffective	Effective	Curative	Effective rates
Pruritus	4a	50	39	96%
Skin elasticity	12	48	33	87%
Skin color	21	52	20	77%

Results

Clinical and Pathological Features of Nnedv Patients in Hifu Treatment

(Table 1) showed the clinical and pathological features of the patients. In total, 93 patients underwent HIFU treatment and were followed up regularly. Among them, 39 patients were diagnosed with lichen sclerosis and 54 lichen simplex chronicus (squamous cell hyperplasia in 1987 ISSVD terminology). The average age of the patients was 41 ± 11 (23~65) years old and the average disease duration was 6 ±

3 (1~11) years. The number of treatments included 1, 2, 3, 4, 61%, 35%, 3%, 1%, respectively. The average treatment time was 113 ± 38 seconds (s) and the average therapeutic dose was 394 ± 117 joule (J).

Therapeutic Effects After Hifu Treatment

For accurate illustration, therapeutic effects were separately analyzed according to different typical symptoms and signs (Table 2). The total effective rate in pruritus is 96% with 39 curative, 50 effective and 4 ineffective cases. The total effective rate in skin elasticity is 87% with 33 curative, 48 effective and 12 ineffective cases. The total effective rate in skin color is 77% with 20 curative, 52 effective and 21 ineffective cases. In addition, the effective rate of sexual satisfaction is 70% (57/82) with 11 patients refusing to answer or denying sexual life. The cumulative recurrence rate of 24% (29/93). In complications, small blisters occurred in 8% (7/93) and spontaneously healed within 14-21 day. And 3% (3/93) developed ulceration on basis of blisters and recovered after symptomatic treatment. In Figure2, this shows the gradual healing process of treatment, Photo(a) was taken before treatment, multiple white lesion areas of the labia majora on the left and right sides.

Photo(b) was taken immediately after treatment, congestion and edema appear in the lesion area of the right labia majora, and the epidermis remains intact. Photo(c) was taken one month after treatment; the pigment island was deposited on the left and right labia majora lesions. Photo(d) was taken 2 months after treatment, it can be seen that the pigment in the lesion area of the right labia majora returned to normal, and the left side was significantly reduced. In Figure3, this is another case of healing process, Photo(e) was taken before treatment, the pigmentation of the right labia majora and the posterior part of the labia majora on the left side was thickened, and the pigmentation of the clitoris. Photo(f) was taken 3 months after treatment, the elasticity of the vulva skin returned to normal. Photo(g) was taken 6 months after treatment, the vulva returned to normal.

Therapeutic Doses Per Unit Area of Hifu Treatment

The average therapeutic dose per unit area (mean ± standard deviation) in all patients was 41 ± 21J/cm2. In effective treatment patients, according to the difference score 3, 2, 1 in pruritus before and after HIFU treatment, the average therapeutic doses per unit area were 27 ± 12, 44 ± 23, 40 ± 20 J/cm2, respectively. Among them, the doses in difference score 3 group (the best curative effect group) were significantly lower than the other two groups (P=0.01, P=0.02), respectively. In ineffective patients, namely difference score 0 (no difference) in pruritus before and after HIFU treatment, the average therapeutic doses per unit area were 36 ± 3 J/cm2.

Discussion

The Terminology History of NNEDV

NNEDV are a group of common vulvar non-infectious, benign dermatoses. Characteristic clinical manifestations include vulvar pruritus, pain, dyspareunia, skin depigmentation, rhagadia, adhesion and atrophy. Epidemiological studies showed that NNEDV may be associated with genetic [10-13] and immune factors [14, 15], however, the etiology remained unknown. Initially, NNEDV was named vulvar leukoplakia, neurodermatitis, etc. In 1976, the International Society for the study of Vulvovaginal Disease (ISSVD) used the word dystrophy as a neutral term to substitute previous nomenclature to clearly separate these benign disorders from the premalignant and malignant epithelial conditions. Dystrophy was subdivided into 3 categories: lichen sclerosus, hyperplastic dystrophy and mixed dystrophy [16]. However, the dermatologists and dermatopathologists recommended elimination of the nomenclature because of its imprecision and lack of usefulness. In 1987, ISSVD discontinued the use of the term dystrophy and replaced with NNEDV, which contained 2 specific categories: (lichen sclerosus and squamous epithelial hyperplasia) and 1 general categories (other dermatoses) [17]. And this classification system remained in use to the present. However, NNEDV was misleading in that many of the conditions were not solely, or even primarily, epithelial. Based on pathologic subsets and their clinical correlates, 2006 ISSVD Classification of Vulvar Dermatoses was then issued, which included 8 histologic patterns: spongiotic pattern, acanthotic pattern (formerly squamous epithelial hyperplasia), lichenoid pattern, dermal homogenization/ sclerosis pattern, vesiculobullous pattern, acantholytic pattern, granulomatous pattern, vasculopathic pattern and a list of the diseases most commonly demonstrating that pattern. Then, using clinicopathologic correlation, the clinician could almost always determine the most likely diagnosis [18]. To assist clinicians to arrive at a diagnosis based solely on clinical findings, ISSVD published 2011 ISSVD Terminology and Classification of Vulvar Dermatological Disorders: An Approach to Clinical Diagnosis. About 50 of the most commonly encountered disorders along with a few uncommon conditions that are so important (e.g., melanoma) were listed in 8 morphological groups. Notably, it does not supplant the 2006 ISSVD Classification of Vulvar Dermatoses, which remains an important tool where a specific clinical and/or biopsy diagnosis is not possible [19].

HIFU Treatment of NNEDV

Topical corticosteroids are the mainstay of therapy and treatment with a superpotent topical corticosteroid, such as 0.05% clobetasol propionate, has long been considered the standard of care. Approximately 89~95% of patients reported improvement of symptoms [20, 21]. In 1927, ultrasound was first described by Loomis and Wood as having a biologic effect on living tissues [22]. Thermal ablation occurs when the targeted delivery of heat or cold causes a rapid change in temperature >55°C for heat or < -20~50°C for cold in the local tissue environment. The ability of focus ultrasound to induce thermal or mechanical effects at focal locations in living tissue has long been recognized; the earliest exploration of the medical use dates to 1942, when Lynn et al first tested it in the brain. Notably, in the 1950s the Fry brothers developed a clinical focus ultrasound device for treating patients with hyperkinetic disorders such as Parkinson disease [23,24]. HIFU is a completely non-invasive thermal ablation technique, which can accurately localize the target tissue by using ultrasound or MR imaging guidance. In particular, MR imaging guidance and MR imaging thermometry allows for accurate targeting, real-time monitoring, and even control of energy deposition. This disruptive technology can revolutionize the various fields of surgery and has replaced partial surgery in breast, liver, prostate cancer etc. In gynecology, focused ultrasound with ultrasound and MR guidance has been approved to treat uterine leiomyomas in Europe and USA, respectively. In the last 20 years, more reports showed HIFU is safe and effective in NNEDV with effective rate of 90~98% and recurrence rate of 9~36% [3, 4, 8, 25, 26]. The treatment was statistically more effective in younger patients with squamous hyperplasia and smaller lesions than in older patients with lichen sclerosus and larger lesions [8].

Characteristics and Mechanism of HIFU Treatment

Skin consists of 3 layers: epidermis, dermis and subcutis. The skin thickness of epidermis and dermis (with exception of subcutis) usually varies from 0.5mm to 4mm, depending on different individuals, ages and sites [27,28]. Since NNEDV involve epidermis and dermis on histologic examination, HIFU treated the skin with the focus of 4~6mm and the depth of <8mm without ultrasound or MR guidance (Figure 1). On one hand, treatment is simple, convenient and low cost. On the other hand, without real-time monitoring and control of energy deposition, clinicians have to determine the treatment time and doses by the size and extent of lesions and the degree of skin edema. Different degrees of swelling and congestion may last for 3~7 days in nearly all patients. Scalding change may appear in a few patients due to nonuniform movement of the probe. Since the judgments of degrees of skin edema to stop treatment were different among clinicians, dramatic differences in treatment time existed in literature, ranging from 8 min to 60 min, with scalding, blisters or ulcer in 2~10% of patients and ulcer in 2~3% of patients [8,25,29]. Compared with the previous studies, the treatment time in our experience was shorter with the average time 2 min (113s, ranging from 1~5min), and the incidence of complication was in accordance. Up to now, there have been no reports on the doses of vulvar HIFU treatment, and shortage of safe, effective and quantified therapeutic dose studies. Lack of standardized treatment protocol is an important factor which hampers its clinical application.

Quantified Experience of Hifu Treatment

Photos of patients is shown below in photo(a) to photo(g). Our data in the past decade show that HIFU is an effective treatment of NNEDV, which is consistent with previous reports in efficacy, recurrence and complication rates3, 4, 8, 25, 26. Based on analyzing respective symptoms and signs after treatment, the efficacy in improving the pruritus were higher than skin color and elasticity. Before HIFU treatment, 39 of 93 patients complained severe pruritus (pruritus score 3). They were severely affected by the intolerable pruritus and often could not sleep at night. After treatment, 11 patients (29%) had no pruritus (pruritus score 0); 19 patients (50%) had mild pruritus (pruritus score 1); 7 patients (18%) had moderate pruritus (pruritus score 2) and only 1 patient (3%) still had severe pruritus (pruritus score 3). In our perspective, the therapeutic doses should correlate with the lesion areas. Therefore, treatment areas, doses, time and other parameters in all patients were recorded in order to study the treatment doses per unit area. The results showed that the safe doses per unit area varied to a great extent (8-92 J/cm2). In the safe range, the doses were not linearly correlated to efficacy. That is, a higher dose is not associated with the better effect. The average dose per unit area 41 ± 22 J/cm2 in effective group and 27 ± 12 J/cm2 in the best effect group (pruritus score 3 before treatment and 0 after treatment). Hence, there remains a relatively wide range in effective or curative doses and future studies are in need to investigate more accurate doses within the range.

Conclusion

HIFU is an effective treatment of NNEDV. In the safe range, a higher dose is not associated with the better effect. Quantified therapeutic doses per unit area may help clinicians make optimal treatment programs and be of great significance for the standardized HIFU treatment.

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Disclosure

No conflict of interest

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