High-intensity focused ultrasound therapy for pediatric and adolescent vulvar lichen sclerosus

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ABSTRACT

Objective: The study’s objective was to retrospectively evaluate the efficacy and safety of high-intensity focused ultrasound (HIFU) for vulvar lichen sclerosus (VLS) in pediatric and adolescent patients.

Methods: Pediatric and adolescent patients presenting to our hospital from June 2007 to July 2021, with VLS were retrospectively evaluated. The participants’ information, including age, symptoms and vulvar examination, were documented, and they were treated with HIFU. The effectiveness of HIFU and its complications were analyzed.

Results: A total of 36 patients with VLS undergoing HIFU for whom complete follow-up data were available participated in the study. The mean age of the patients at diagnosis was 13.3 ± 4.1 years. All patients successfully underwent HIFU therapy. The mean sonication time was 20.3 ± 8.6 min, and the median treatment energy was 3579.0 J. A few blisters developed in 8 (22.2%) patients and 2 (5.6%) had ulcers. The skin burns were treated medically without scar formation. On average, patients were followed up for 52.0 months after the procedure (a range of 6–175 months). At 6 months after therapy, the total response rate was 91.6%, and 86.6% at 12 months post HIFU. Overall, 16 patients were followed up for more than 5 years. The total response rate was 75%, and the recurrence rate was 12.5%.

Conclusions: Based on our results, HIFU was demonstrated to be effective and relatively safe for the treatment of VLS in pediatric and adolescent patients, but it is necessary to pay attention to the possible skin burns.

Introduction

Vulvar lichen sclerosus (VLS) is a chronic inflammatory disease, and its etiology is unclear and complex. It has a bimodal starting age, in prepubertal and postmenopausal age groups. There is a clear peak of incidence in girls aged four to six years old, which represents 7–15% of all VLS cases [1]. The main clinical manifestations are vulvar pruritus, irritation and pain, bleeding due to skin fissures and constipation [2,3]. Urinary tract symptoms, including dysuria, holding urine for fear of voiding and overflow incontinence may also be presenting features [4]. VLS has also been associated with a reduced quality of life among premenarchial girls. Since the symptoms of VLS can mimic other conditions, it is often initially misdiagnosed [5], and its diagnosis in girls is often delayed by an average of 1–2 years from the onset of symptoms to a final diagnosis. However, early diagnosis and treatment are crucial in improving symptoms and reducing the long-term sequelae of scarring.

The goals of the treatment of VLS in pediatric and adolescent patients include relieving symptoms, resolving atrophic changes and preventing scarring and anatomic distortion. To our knowledge, there have been no randomized controlled trials for VLS therapy in children and adolescents. The mainstay of treatment, currently, is topical high potency corticosteroids and, alternatively, topical immune modulators, which have been advocated as the treatment of choice for VLS in adults based on reports affirming their safety and efficacy [2]. However, recurrences are common after corticosteroids treatment [6]. Prolonged use of topical steroids can be associated with thinning of the dermis, secondary superimposed infections and rarely hypothalamic–pituitary–adrenal axis suppression [7]. It is particularly important to find minimally invasive and effective treatment methods.

High-intensity focused ultrasound (HIFU) has received increasing attention as a nonsurgical treatment for gynecological diseases [8]. Several studies have demonstrated the safety and effectiveness of HIFU for the treatment and management of vulvar dermatoses in adults [9–11]. However, studies on the application of HIFU for VLS in childhood and adolescence are rare. We have treated more than 3000 non-neoplastic epithelial disorders of the vulva in patients since 2006. These include a few children and adolescents with VLS. Thus, the current study’s objective was to retrospectively evaluate the efficacy and safety of HIFU for VLS in childhood and adolescence.
Materials and methods

The protocol of this retrospective study was approved by the institutional board of the Third Xiangya Hospital of Central South University (No. 21002), and the requirement for an informed consent to do the research was waived.

Patients

We performed a retrospective evaluation of pediatric and adolescent patients with VLS who were treated with HIFU in the Department of Obstetrics and Gynecology at the Third Xiangya Hospital of Central South University between June 2007 and July 2021. The inclusion criteria were as follows: (1) patients who were 18 years of age or younger at the time of diagnosis; (2) patients diagnosed with VLS according to the diagnostic standard (significant vulvar pruritus with skin discoloration and atrophy) [12]; (3) patients who did not receive physicotherapeutics or topical corticosteroids in the last three months before HIFU; and (4) patients treated with HIFU at our hospital. Data on age at onset, menstruation, symptoms, vulvar examination, previous treatments, treatment parameters, therapeutic effect and complications were collected from a review of electronic medical records and telephone interviews.

HIFU therapy

Detailed treatment procedures have been described in our previous study [9]. In brief, after local infiltration anesthesia using lidocaine or intravenous anesthesia (used in seven children aged 4–10 years who could not receive local anesthesia) was administered, HIFU treatment was applied. Its output power was set to Level 2 (3 W) or Level 3 (3.5 W), which was the power commonly used in HIFU therapy. During the treatment, the probe was in close contact with the skin above the lesion and the healthy tissues within 5 mm of the area of the lesion through an ultrasound couplant. The therapy was deemed complete when the treatment area showed mild congestion, swelling and hyperthermia. Ice packs were intermittently applied to the treated area for 12–24 h. At the same time, moist burn ointment was applied intermittently to the treated area.

Follow-up

Patients were followed up at the outpatient clinic 1 week after treatment to check for skin complications. Potential complications, including blisters, ulcers, scleroma and infection were recorded. Subsequently, outpatient checkups were conducted at 1, 3, 6 and 12 months after treatment, and every 6 to 12 months thereafter. The treatment responses were classified as curative (symptoms such as vulva pruritus disappeared, skin color and elasticity of the diseased area became normal), effective (symptoms decreased and vulva skin color and elasticity partially recovered) or ineffective (symptoms continued and signs of local skin did not change) based on the patients’ responses to the therapy. The sum of the cure rate and the effective rate is the total response rate, which is the primary study outcome. Recurrence was defined as an exacerbation of symptoms after complete remission or a worsening of symptoms after a period of improvement.

Statistical analysis

The Statistical Program for the Social Sciences version 22.0 (SPSS Inc., Chicago, IL, USA) was used to calculate the descriptive statistics. The normally distributed continuous data were presented as the mean ± standard deviation, and the abnormally distributed continuous data were presented as the median and range. The categorical data are presented as the frequency and percentage.

Results

Baseline characteristics

A total of 43 patients met the inclusion criteria, but 7 patients did not have complete follow-up data. Finally, 36 patients were enrolled in this study. Before HIFU treatment, we informed each patient and guardian that they could choose topical glucocorticoids therapy, but all patients chose HIFU treatment mainly because of concerns about the side effects of topical glucocorticoids therapy. The demographic and clinical characteristics of all 36 patients with VLS are described in Table 1. The mean age of the patients at the time of diagnosis was 13.3 ± 4.1 years, while the age range was 4–18 years. The duration of the disease was 0.1–12 years (2 years on average). The starting age of the disease was 10.9 ± 3.8 years. There were 18 prepubertal and 18 postmenarchal girls. The most common symptoms included pruritus and vulvar irritation, and the most common physical

| Symptom          | Values     |
|------------------|------------|
| Lesion size/vulva size | 36 (100.0) |
| Hypopigmentation  | 36 (100.0) |
| Fissures         | 4 (11.1)   |
| Scarring          | 11 (30.6)  |
| Erythema          | 2 (5.6)    |
| Lesion involves the anal | 11 (30.6) |
| Yes              | 25 (69.4)  |
| No               | 25 (69.4)  |

Values are given as n (%) unless otherwise stated.

Table 1. The demographic and clinical characteristics of patients with vulvar lichen sclerosus.
examination findings included hypopigmentation and scarring. In 11 (30.6%) cases, the lesion involved the perianal area. Of the patients, 20 were treated with traditional Chinese medicine, but there was no obvious effect, and 12 had received irregular topical corticosteroid therapy and their symptoms were partially relieved. The condition was diagnosed incorrectly in 19 (52.8%) patients at the gynecology outpatient department of other hospitals.

**Results of HIFU therapy**

All patients successfully underwent HIFU therapy. The results pertaining to the treatment are shown in Table 2. The device output power in 26 (72.2%) patients was set at level 2, and in 10 (27.8%) patients it was set at Level 3. The sonication time was 20.3 ± 8.6 min, and the median treatment energy was 3579.0 J. A few blisters developed in eight (22.2%) patients, of which two patients developed superficial skin ulcers. About 1 week after the treatment, the six patients who had a few blisters in the vulvar treatment area improved after topical treatment with moist burn ointment without obvious pain, infection and scar formation. An 18-year-old patient was treated with output power Level 2 for 10 min and 15 s, with a total energy of 1393 J. On the seventh day of treatment, multiple ulcers and inflammatory exudation were found during the outpatient follow up review. The patient was given anti-infection treatment, moist burn ointment and epidermal growth factor, which were applied externally, and the wound healed 1 month after treatment. Another 8-year-old child was treated with HIFU for 8 min with an energy of 1494 J. A few blisters appeared immediately after therapy. One week later, multiple superficial ulcers were seen in the treatment area. Mupirocin was given as a local anti-infection treatment. Moist burn ointment and epidermal growth factor were also applied. The wound healed within 1 month of treatment without scar formation.

**Follow-up results**

On average, patients were followed up for 52.0 months after the procedure (a range of 6–175 months). The efficacy results of HIFU therapy are shown in Table 2. At 6 months after therapy, 21 (58.3%) patients were cured, 14 (33.3%) significantly improved and 3 (8.4%) therapies were ineffective. The total response rate was 91.6%. Of the 30 patients who were followed-up for more than 1 year, 16 (53.3%) were cured, 10 (33.3%) improved significantly and 2 (6.7%) therapies were ineffective. The total response rate was 86.6%, and the recurrence rate was 6.7%. In addition, 16 patients were followed up for more than 5 years, 8 patients were cured, 4 improved, 2 did not respond and 2 relapsed. The total response rate was 75%, and the recurrence rate was 12.5%. Among them, a 15-year-old patient received first treatment with HIFU in July 2009, and her symptoms improved significantly. In May 2013, the itching symptoms recurred, and she received the second treatment of HIFU, and the itching symptoms disappeared later. Another patient, a 17-year-old female, received her first HIFU treatment in June 2012 and experienced relief from itching. In April 2017, the itching symptoms became significantly worse, and the second HIFU treatment was performed in July 2017, and the patient was cured thereafter.

**Discussion**

VLS presents with a range of signs and symptoms. Due to nonspecific clinical manifestations, early diagnosis is difficult, and it may take several years between the patient’s first presentation and the correct diagnosis [13]. Pruritus and vulvar irritation were found to be the most common presenting symptoms, with hypopigmentation and scarring the most frequent signs in our cohort of patients. This is similar to findings in other studies [1,3]. One single study indicated that 10 out of 15 (66%) girls with VLS presented with perianal lesions, and the incidence of perianal lesions was much higher in female patients, including children [14]. In our study, there were 11 (30.6%) cases in which the lesion involved the perianal area. Compared with previous studies, this is relatively low.

This study reveals that the starting age of the disease is 10.9 ± 3.8 years; however, the mean age of the patients at the time of diagnosis was 13.3 ± 4.1 years, which is contrary to other reports [4,15]. Some 19 (52.8%) patients were diagnosed incorrectly in the gynecology department of other hospitals. The rate of delayed diagnosis is consistent with other studies. Lagerstedt et al. claimed that only 16% of those with VLS are diagnosed in the early stage of the disease [16]. Possible causes for the underdiagnosis of VLS, particularly in children and adolescents, are the relative inexperience by pediatricians and gynecologists in dealing with vulvar conditions, lack of parental awareness about the significance of the reported symptoms and the reluctance of the girls to complain of pruritus in the genital area.

| Variables | Values |
|-----------|--------|
| Sessions of HIFU | 1 |
| Success of HIFU | 36 (100.0) |
| Sonication time (min) | 20.3 ± 8.6 |
| Power | Level 2 26 (72.2) Level 3 10 (27.8) |
| Treatment energy (J) | 3579.0 (1380.0, 8160.0) |
| Adverse effects | Blister: 8 (22.2%), Ulcer: 2 (5.6%) |
| Efficacy | Six months after HIFU: Curative 21 (58.3%) Effective 12 (33.3%) Ineffective 3 (8.4%) Twelve months after HIFU: Curative 16 (53.3%) Effective 10 (33.3%) Ineffective 2 (6.7%) Recurrence 2 (6.7%) Five years after HIFU: Curative 16 Effective 8 (50.0%) Ineffective 4 (25.0%) Recurrence 2 (12.5%) |

Values are given as n (%) unless otherwise stated.
In females, VLS may lead to obliteration of the labia minora and clitoris or narrowing of the vaginal introitus, urinary retention, urinary incontinence and recurrent urinary tract infections when VLS in children has a delayed diagnosis or is misdiagnosed, which can be detrimental to the patient [17]. Nearly half of the children diagnosed with VLS had irreversible atrophic genital skin changes at the time of the first presentation. These changes may have been prevented by a timely diagnosis and intervention [1]. Awareness of VLS is paramount; Wang et al. showed that the SWIFT Model comprising five clinical parameters: soreness (S), whitening (W), urinary incontinence (I), fissures (F) and thickening of the clitoral hood (T) will prove invaluable in assessing timely diagnosis and treatment for premenarchal patients. This model was confirmed through testing in a larger cohort of girls with an accuracy of 97% and may lead to greater adoption among the clinical community [18].

In children, the current recommended treatment regimen is daily topical high-potency corticosteroids for several months, followed by a tapering application. The corticosteroid treatment is recommended to maintain normality of skin color and texture and to prevent scarring in patients with VLS [19] and it led to a significant decrease in the undesirable impact of VLS on patients’ well-being [20]. Women with VLS improve more when topical steroids are used exactly as prescribed, though some improvement occurs with imperfect use [21]. Compliance with corticosteroid therapy appears to be critical in the prognosis of pediatric VLS, although attitudes underpinning noncompliance to corticosteroid treatment require further elucidation. However, compliance is a complex entity in the pediatric and adolescent cohort [22]. A prospective cohort of girls with a prepubertal diagnosis of VLS noted to have poor compliance developed irreversible loss of labia minora and clitoral phimosis [23]. Thinning of the epidermis and secondary infections are potential side-effects of local corticosteroid use. Concerns regarding safety of corticosteroids were among the most commonly reported reasons for nonadherence to treatment among the patients [24]. In addition, the recurrence rate of prepubertal VLS after initial treatment with local potent corticosteroids has been reported to range from 44% to 82%, which is relatively high [23]. In this study, 12 patients had received irregular topical corticosteroid therapy and their symptoms were partially relieved; however, they were not willing to take corticosteroid therapy for a long time.

Some other therapies have recently been studied for the treatment of VLS in adult patients, including photodynamic therapy (PDT) [25], fractional ultrapulsed CO2 laser [26], HIFU and mixed methylene blue compound injection [27]. However, none of these treatments have been reported for pediatric and adolescent patients. HIFU stimulates cell proliferation, protein synthesis and reverization, thereby accelerating tissue reconstruction [28]. After HIFU treatment, vulvar tissue structures recovered their normal pigmentation, the count of microvessels increased, their lumens recovered and nerve endings and fibroblast counts in the lower layer of the dermis increased [10]. We have treated more than 3000 non-neoplastic epithelial disorders of vulva patients since 2006. HIFU was effective in alleviating symptoms and improving vulvar signs, with a cure rate of 42.2%, an effective rate of 56.1% and a low recurrence rate of 9.4% [11]. However, studies on the application of HIFU for VLS in childhood and adolescence are rare. In this study, we treated 36 pediatric and adolescent patients with HIFU. The results confirmed that HIFU has a good effect on the treatment of adolescent VLS.

Although HIFU treatment is relatively safe, the vulva of children and adolescents is not fully developed, and the skin is tender. Therefore, possible skin burns, including severe skin damage or coagulative necrosis to HIFU, are also a concern. In previous studies, the probability of mild skin burns in adult patients treated with HIFU ranged from 8.8% to 23.3%, which was related to the output power of HIFU [9,29]. In this study, considering the nature of vulvar skin in young patients, the majority of patients who received HIFU did so at a low power output level. There were eight (22.2%) patients had blisters after the treatment. The results indicate that children and adolescents are more prone to skin injury than adults, even though the degree of skin burns is mild. All patients were cured by moisture-exposed burn ointment without vulvar scar formation.

Our study has multiple limitations, including its retrospective design, absence of a control group or randomization. Although this study showed that HIFU was effective and safe in the treatment of VLS in pediatric and adolescent, this study did not compare the safety or efficacy of HIFU with the standard first-line therapy or second-line therapy. In addition, due to the small sample size, this study did not explore any possible factors (i.e. HIFU duration, power deposition, patient characteristics, etc.) that could be associated with either immediate or relatively long-term adverse effects. This study also involved only pediatric and adolescent females and was conducted at a single institution. Larger prospective studies will be necessary to determine the efficacy and safety of HIFU in treating VLS compared with patients treated with only topical corticosteroids and analyze the factors affecting the efficacy and safety.

Conclusion

In summary, HIFU has definite efficacy in treating VLS in pediatric and adolescent patients. It causes little damage to the lesioned tissue, has a good safety profile and leads to a few complications.

Author contributions

H.S.L. assembled the data and drafted the manuscript. J.F.J conceived the idea for the study, carried out the analyses and reviewed and revised the manuscript.

Disclosure statement

All authors declare no conflict of interests.
Funding
The Wisdom Accumulation and Talent Cultivation Project of the Third Xiangya Hospital of Central South University [No. YX202112].

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