



Combined therapy of local recombinant human interferon α 1b injection and acupuncture on verruca vulgaris: a retrospective study

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Abstract

Verruca vulgaris is always stubborn to treat. We applied a new combined therapy of local recombinant human interferon alpha 1b (rhIFN α 1b) injection plus acupuncture on verruca vulgaris recently to evaluate the efficacy and safety of the combined therapy. The retrospective study was conducted in The First Hospital of China Medical University from 2018 to 2020. Patients with verruca vulgaris were included. Combined therapy with local rhIFN α 1b injection plus acupuncture was set as treatment group, rhIFN α 1b injection and carbon dioxide (CO₂) laser were set as control groups. A total of 2415 patients were included in the study. The cure rates were 81.85%, 85.93%, and 100% in combined group, rhIFN α 1b group, and CO₂ laser group, separately. All lesions cured in combined group were located on hands or feet, while majority of lesions cured in other groups were located on other sites. For patients with medium/big single lesion or 6–9 lesions, less treatment times were needed in combined group than rhIFN α 1b group. For patients with small single, two to five or more than ten lesions, the treatment times of combined group and rhIFN α 1b group were comparable. All patients complained of pain in varying degrees when local injection or laser irradiation. Compared with CO₂ laser group, more fever, less swelling or scar was reported in combined group. In conclusion, combined therapy of local rhIFN α 1b plus acupuncture was beneficial for verruca vulgaris with limited adverse effects. The therapy was more acceptable by younger female patients with verruca vulgaris.

Keywords Recombinant human interferon alpha 1b (rhIFN α 1b) · Acupuncture · Verruca vulgaris · Human papillomavirus (HPV)

Introduction

Verruca vulgaris, also named as common wart, is a benign skin disorder infected by human papillomavirus (HPV). It is characterized by acanthosis, papillomatous hyperplasia,

hyperkeratosis, and parakeratosis in epidermis. The population prevalence rate ranges from 7 to 10% worldwide [1]. Verruca vulgaris usually locates on hands or feet, but sometimes on arms or legs. Various modalities have been applied for verruca vulgaris, such as ablation of warts (cryosurgery, laser, electrodesiccation, salicylic acid, silver nitrate, imiquimod, and trichloroacetic acid), interruption of the organic process (podophyllotoxin, intralesional bleomycin, and 5-fluorouracil), and surgical excision. However, most of the therapies are invasive, painful or inclined to relapse [2]. Therefore, more alternative modalities are urgently needed.

Interferon (IFN) is an important protein discovered in 1957 [3]. It is beneficial to anti-virus and immune regulation [4]. There are three types of IFNs, including Type I (IFN α , IFN β), Type II (IFN γ), and Type III (IFN λ). IFN α arises from plasmacytoid dendritic cells, it upregulates genes involved in immune processes by recognizing microbial nucleic acids/immune complexes and binding to Type I IFN receptor, thus restricts viral replication and enhances

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B cell responses [5]. IFN α 1b has been applied to some viral diseases and malignant tumors. It ameliorates symptoms of neonatal respiratory syncytial virus pneumonia with minimal adverse effects [6] and prolongs survival time of patients with unresectable metastatic melanoma [7]. Combined therapy of arbidol and IFN α 1b decreases the severity of moderate COVID-19 pneumonia [8]. Recombinant human IFN α 1b (rhIFN α 1b) is a kind of genetic engineering IFN. Early use of rhIFN α 1b in hospitalized infants with lower respiratory tract infections (viral pneumonia, wheezy bronchitis, or bronchiolitis) could prevent subsequent wheezing [4]. rhIFN α 1b gradually regressed lesions of a patient diagnosed as subcutaneous panniculitis-like T cell lymphoma without relapsing in the 10-month follow-up [9]. In general, IFN α 1b is injected subcutaneously or intramuscularly. To obtain higher local concentration, intralesional injection has also been tried. Zeng et al. reported a successful case of cutaneous pseudolymphoma on the nose with combination of intralesional IFN α 1b and compound betamethasone [10].

Acupuncture is a traditional Chinese therapy with a long history of more than 3000 years. It is effective for numerous disorders, such as inflammation, pain [11], and psychosocial abnormalities (anxiety, depression) [12]. Acupuncture is a relatively safe complementary and alternative nonpharmacological therapy [13]. The potential mechanisms might be stimulating meridians of human body, regulating blood circulation and improving immune function [14]. Recently, it has been applied to several dermatoses, such as psoriasis, atopic dermatitis, urticaria, and pruritus [15, 16]. Ursini et al. reported that a chronic HPV wart patient with HIV infection who was resistant to cryotherapy was cured after 58 sessions of systemic acupuncture over 19 months [17]. To our knowledge, no intralesional acupuncture application has been reported in dermatoses till now.

In the past 3 years, we innovatively applied a combined therapy of local intralesional rhIFN α 1b followed by acupuncture to patients with verruca vulgaris and obtained satisfied effects. Herein, we retrospectively reported the efficacy and safety of the combined therapy.

Methods

Patients with verruca vulgaris treated at outpatient clinic of Department of Dermatology, The First Hospital of China Medical University from January 1, 2018 to December 31, 2020 were included in the present retrospective study. Patients treated with combined therapy of local intralesional rhIFN α 1b (Tri-Prime Gene, Beijing, China) followed by intralesional acupuncture was set as treatment group, those with local intralesional rhIFN α 1b or carbon dioxide (CO₂) laser were set as control groups, separately. For the combined group and rhIFN α 1b group, rhIFN α 1b

was injected intralesionally for each lesion. Subsequently, acupuncture needles were injected into the bottom of the biggest one or two lesions (20 needles/lesion), and were extracted 30 min later. The procedure was repeated at an interval of 7–10 days. Oral immune modulator (pidotimod, thymosin or transfer factor), or topical imiquimod cream was additionally added according to individual conditions. Oral immune modulators were taken for 1–3 months according to the drug instructions, whereas imiquimod was topically applied on the lesions every other day till the lesions were disappeared. For CO₂ group, CO₂ laser was applied to all lesions as described previously [18].

Location, number, and size of the lesions, age and gender of the patients, and treatment sessions were collected. Digital photographs were taken with a camera at focal distance of 1.5 m (Canon 60D, Japan) every time before treatment until the lesions were disappeared and 1, 2, 3 months after the last treatment. Two blinded dermatologists individually evaluated the clinical improvements. Cure was defined as “all lesions were disappeared”. Cure rate was calculated by dividing the number of cured patients with that of all patients in the specific group. Any adverse effect during or after treatment, such as fever, swelling, hyperpigmentation, scar or infection, was reported by the patients and recorded by the dermatologists. The recurrence rate was evaluated 3 months after the last treatment.

All data were analyzed by GraphPad Prism version 9.0.0 (GraphPad Software, San Diego, California, USA). Chi-squared test and one-way ANOVA were performed to compare the differences between different groups. $P < 0.05$ was considered as statistically significant.

Results

A total of 2415 patients with average age of 30.62 ± 14.34 years were included in the study. Cured patients in combined group (28.87 ± 12.40 years) was younger than those in CO₂ laser group (34.93 ± 16.00 years) ($P < 0.05$), but comparable with rhIFN α 1b group (27.72 ± 14.16 years) ($P > 0.05$, Table 1). The cure rates were 81.85% (929/1135), 85.93% (464/540), and 100% (740/740) in combined group, rhIFN α 1b group, and CO₂ laser group, separately. The lesions of 781, 1109, 243 patients were, respectively, located on hands, feet, and other sites (arms and legs) in the three groups. Lesions cured by combined group were all located on hands or feet, while majority of lesions cured by other methods were located on arms or legs ($P < 0.05$, Table 1). For gender comparison, there was no statistical significance between combined group and rhIFN α 1b group ($P > 0.05$), but more male patients were seen in CO₂ laser group ($P < 0.05$).

Table 1 Age, gender, and lesion location of included patients

	All, n		Cured patients		Gender, n (%)		Lesion location, n (%)				
	Age		Mean ± SD		Male	Female	Hands	Feet	Others	P	
	n (%)	p		p							
All	2415	2133 (88.32)	30.62 ± 14.34	–	1103 (51.71)	1030 (48.29)	–	781 (37.08)	1109 (51.99)	243 (11.39)	–
1. rhIFNα1b ¹ + acupuncture	1135	929 (81.85)	28.87 ± 12.40	–	419 (45.10)	510 (54.90)	–	369 (39.72)	560 (60.28)	0	–
① -	744	611 (82.12)	28.84 ± 12.43	–	270 (44.19)	340 (55.65)	–	260 (42.55)	351 (57.48)	0	–
② + Oral immune modulator	72	62 (86.11)	30.74 ± 12.34	0.4345*	26 (41.94)	36 (58.06)	0.7889*	12 (19.36)	50 (80.65)	0	–
③ + topical imiquimod	319	256 (80.25)	28.48 ± 12.34	0.0991*	122 (47.66)	134 (52.34)	0.3701*	97 (37.89)	159 (62.11)	0	–
2. rhIFNα1b	540	464 (85.93)	27.72 ± 14.16	0.3529 [#]	190 (40.95)	274 (59.05)	0.1520 [#]	167 (35.99)	239 (51.51)	58 (12.50)	< 0.0001 [#]
① -	266	238 (89.47)	27.42 ± 14.03	–	94 (39.50)	144 (60.50)	–	82 (34.45)	113 (47.48)	43 (18.07)	–
② + oral immune modulator	26	23 (88.46)	28.52 ± 12.09	0.9742 [^]	9 (39.13)	14 (60.87)	> 0.9999 [^]	6 (26.09)	14 (60.87)	3 (13.04)	0.4703 [^]
③ + topical imiquimod	248	203 (81.85)	27.97 ± 14.59	0.9638 [^]	87 (42.86)	116 (57.14)	0.4975 [^]	79 (38.92)	112 (55.17)	12 (5.91)	0.0006 [^]
3. CO ₂ laser	740	740 (100)	34.93 ± 16.00	< 0.0001 [#]	495 (66.89)	245 (33.11)	< 0.0001 [#]	245 (33.11)	310 (41.89)	185 (25.00)	< 0.0001 [#]

¹rhIFNα1b: recombinant human IFN alpha 1b

* Indicates P value comparing with rhIFNα1b + acupuncture group (1.⊙)

[#] Indicates P value comparing with rhIFNα1b + acupuncture group (1)

[^] Indicates P value comparing with rhIFNα1b group (2.⊙)

Sessions of single lesion

There were 929, 464, and 740 patients with single lesion included in the present study in combined group (Figs. 1, 2), rhIFN α 1b group (Fig. 3), and CO₂ laser group (Fig. 4), separately.

For small lesions (diameter < 5 mm), there was no statistical difference in sessions between combined group (4.40 ± 3.94 sessions) and rhIFN α 1b group (4.61 ± 2.37

sessions) ($P > 0.05$). The sessions of both groups were more than those of CO₂ laser group (1 session) ($P < 0.05$). For subgroup analyses in combined group, no statistical difference between rhIFN α 1b + acupuncture only group and rhIFN α 1b + acupuncture + imiquimod group was found. For subgroup analyses in rhIFN α 1b groups, there were no statistical significances between rhIFN α 1b + immune modulator group/rhIFN α 1b + imiquimod group and rhIFN α 1b group ($P > 0.05$) (Table 2).

Fig. 1 Clinical photographs of a patients with verruca vulgaris on left hand treated with rhIFN α 1b, acupuncture, and imiquimod. rhIFN α 1b plus acupuncture was applied every 7–10 days for five times, and imiquimod was applied topically every other day for 2 months

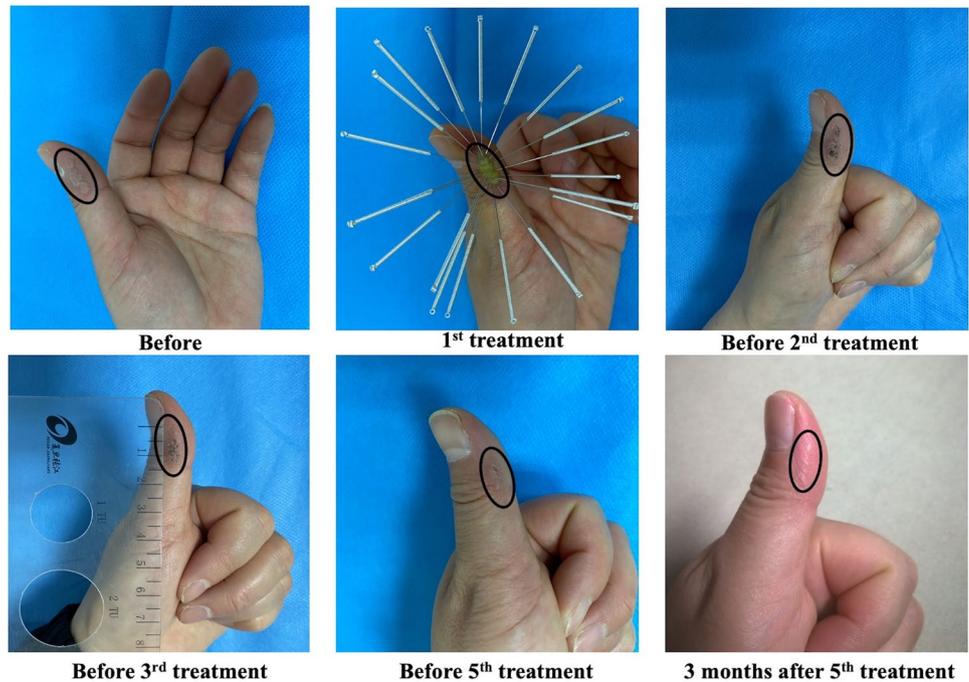


Fig. 2 Clinical photographs of a patients with verruca vulgaris on left foot treated with rhIFN α 1b, acupuncture, and immune modulator (pidotimod). rhIFN α 1b plus acupuncture was applied every 7–10 days for five times, and pidotimod was orally taken 0.8 mg bid for 2 months

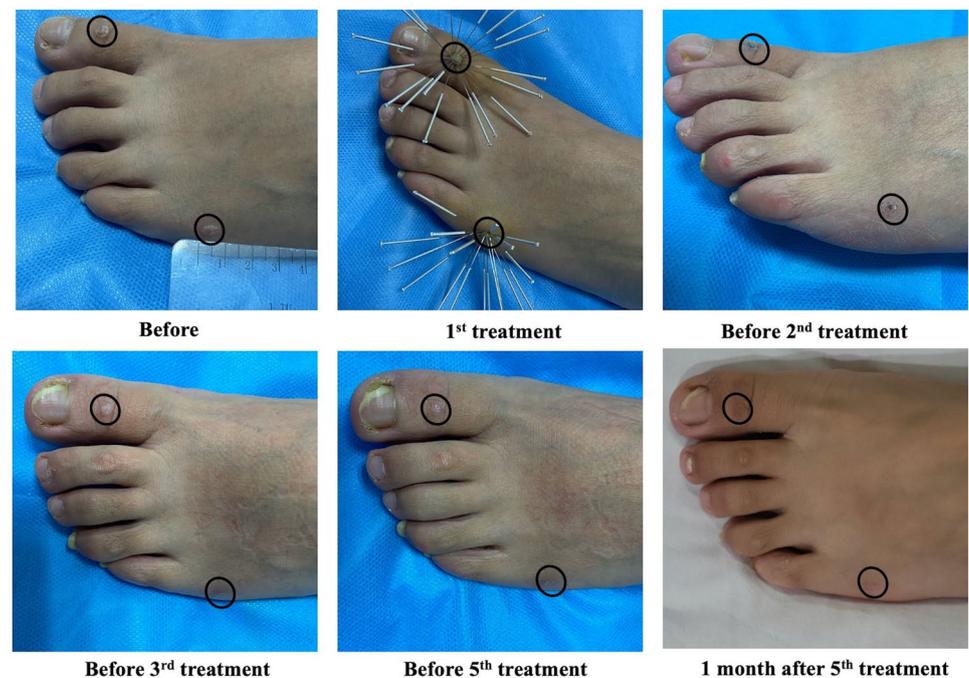


Fig. 3 Clinical photographs of a patients with verruca vulgaris on left foot treated with rhIFN α 1b and imiquimod. rhIFN α 1b was applied every 7–10 days for six times, and imiquimod was topically applied on the lesion every other day for 1.5 months

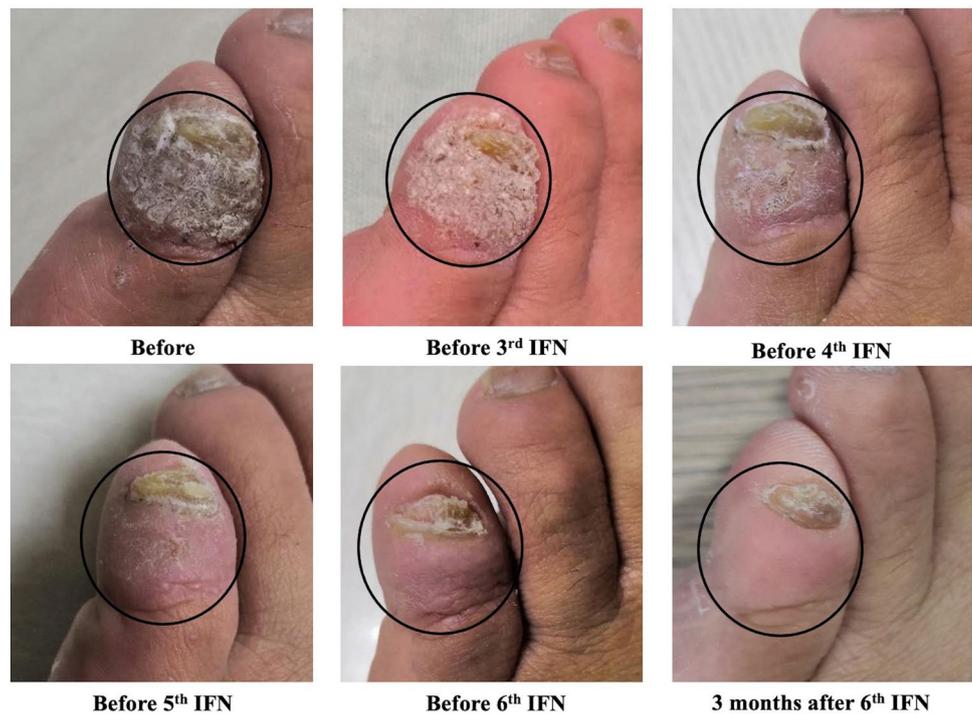
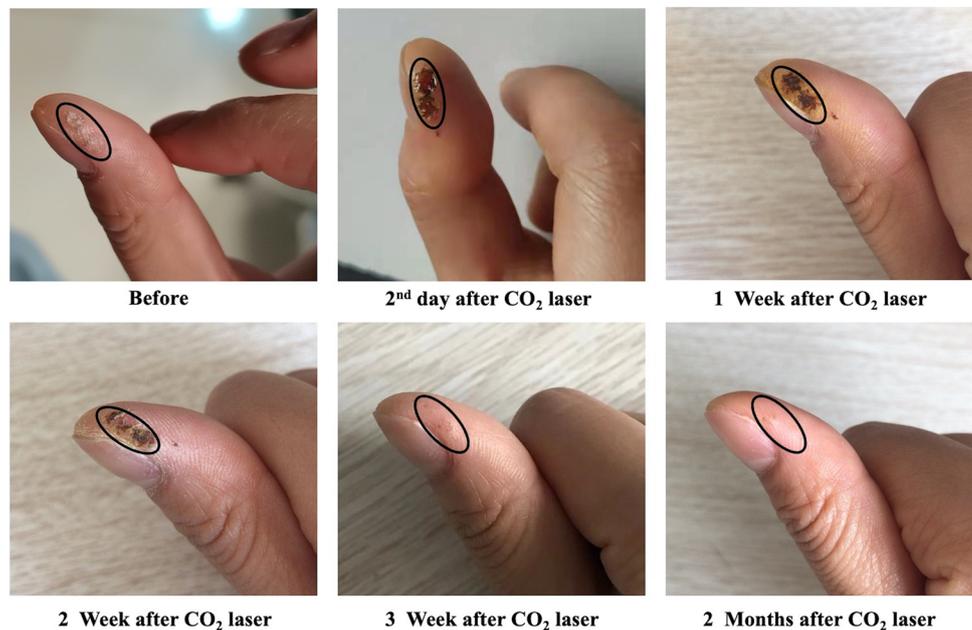


Fig. 4 Clinical photographs of a patients with verruca vulgaris on right hand treated with CO₂ laser once



For medium lesions (diameter 6–10 mm), less sessions were needed in the combined group (5.94 ± 3.38 times) than those in rhIFN α 1b group (9.90 ± 3.86 times) ($P < 0.05$). The sessions in both groups were more than those of CO₂ laser group (1.10 ± 0.30) ($P < 0.05$). There was no statistical difference in combined group for subgroup analyses (rhIFN α 1b + acupuncture only group vs. rhIFN α 1b + acupuncture + immune modulator group, rhIFN α 1b + acupuncture only group vs. rhIFN α 1b + acupuncture + imiquimod

group) ($P > 0.05$). For rhIFN α 1b subgroups, the sessions in rhIFN α 1b only group (10.06 ± 3.32) were more than those in rhIFN α 1b + immune modulator group (5.75 ± 1.63) ($P < 0.0001$), while there was no statistical difference between rhIFN α 1b only group and rhIFN α 1b + imiquimod group (11.40 ± 4.13) ($P > 0.05$) (Table 2).

For big lesions (diameter > 11 mm), less sessions in combined group (8.94 ± 4.42 times) were needed than those in rhIFN α 1b group (12.33 ± 4.71 times, $P < 0.05$). The sessions

Table 2 Treatment sessions of different therapies (mean ± SD)

Groups	Single lesion						Plural lesions					
	Small (< 5 mm)		Medial (6–10 mm)		Big (> 11 mm)		2–5		6–9		> 10	
	n (%)	Sessions (p)	n (%)	Sessions (p)	n (%)	Sessions (p)	n (%)	Sessions (p)	n (%)	Sessions (p)	n (%)	Sessions (p)
1. rhIFNα1b ¹ + acupuncture	461 (49.62)	4.40 ± 3.94 (-)	418 (90.67)	5.94 ± 3.38 (-)	14 (3.04)	8.94 ± 4.42 (-)	468 (50.38)	340 (72.65)	84 (17.95)	6.73 ± 3.70 (-)	44 (9.40)	10.67 ± 4.52 (-)
⊖ -	321 (52.54)	4.23 ± 3.79 (-)	290 (90.34)	6.17 ± 3.29 (-)	13 (4.05)	9.63 ± 4.66 (-)	290 (47.46)	191 (65.86)	62 (21.38)	6.23 ± 3.68 (-)	37 (12.76)	11.71 ± 4.69 (-)
⊕ + oral immune modulator	20 (32.26)	-	20 (100)	5.64 ± 3.76 (0.3482*)	0	-	42 (67.74)	33 (78.57)	7 (16.67)	7.54 ± 4.51 (0.1129 ^b)	2 (4.67)	11.50 ± 0.50 (0.1032 ^c)
⊕ + topical imiquimod	120 (46.88)	4.85 ± 4.27 (0.8479*)	108 (90.00)	5.41 ± 3.47 (0.1384*)	1 (0.83)	8 (-)	136 (53.13)	116 (85.29)	15 (11.03)	6.80 ± 3.72 (0.3541 ^d)	5 (3.68)	7.40 ± 3.20 (0.0678 ^e)
2. rhIFNα1b	196 (42.24)	4.61 ± 2.37 (0.4849 ^f)	44 (22.45)	9.90 ± 3.86 (< 0.0001 ^g)	12 (6.12)	12.33 ± 4.71 (< 0.0001 ^h)	268 (57.76)	220 (82.09)	32 (11.94)	6.66 ± 3.60 (> 0.9999 ⁱ)	16 (5.97)	10.87 ± 3.48 (0.8727 ^h)
⊖ -	110 (46.22)	4.50 ± 2.41 (-)	31 (28.18)	10.06 ± 3.32 (-)	6 (5.45)	10.83 ± 3.07 (-)	128 (53.78)	113 (88.28)	9 (7.03)	7.02 ± 3.64 (-)	6 (4.69)	10.00 ± 3.55 (-)
⊕ + oral immune modulator	7 (30.44)	5.67 ± 1.24 (0.2308 ^j)	4 (57.14)	5.75 ± 1.63 (< 0.0001 ^k)	0	-	16 (69.57)	11 (68.75)	4 (25.00)	7.30 ± 2.49 (0.8795 ^l)	1 (6.25)	9 (-)
⊕ + topical imiquimod	79 (38.92)	4.68 ± 2.21 (0.9437 ^m)	9 (11.39)	11.40 ± 4.13 (0.1332 ⁿ)	6 (7.59)	13.83 ± 5.52 (0.2139 ^o)	124 (61.08)	96 (77.42)	19 (15.32)	6.04 ± 3.58 (0.9564 ^p)	9 (7.26)	11.75 ± 3.38 (0.1329 ^q)
3. CO ₂ laser	579 (78.24)	1 (< 0.0001 ^r)	68 (11.74)	1.10 ± 0.30 (< 0.0001 ^s)	22 (3.80)	1.23 ± 0.42 (< 0.0001 ^t)	161 (21.76)	161 (100)	0	1.08 ± 0.27 (< 0.0001 ^u)	0	-

¹rhIFNα1b: recombinant human IFN alpha 1b

*Indicates P value comparing with rhIFNα1b + acupuncture group (1.⊖)

#Indicates P value comparing with rhIFNα1b + acupuncture group (1)

^Indicates P value comparing with rhIFNα1b group (2.⊖)

of both groups were more than those in CO₂ laser group (1.23 ± 0.42 times) ($P < 0.05$). For rhIFN α 1b subgroups, there was no statistical difference between rhIFN α 1b only group (10.83 ± 3.07) and rhIFN α 1b + imiquimod group (13.83 ± 5.52) ($P > 0.05$) (Table 2).

Sessions of plural lesions

There were 468, 268, and 161 patients with plural lesions included in the present study in combined group, rhIFN α 1b group, and CO₂ laser group, separately.

For patients with 2–5 lesions, there was no statistical difference in sessions between combined group (6.25 ± 3.64 times) and rhIFN α 1b group (6.66 ± 3.60 times) ($P > 0.05$). The sessions in both groups were more than those of CO₂ laser group (1.08 ± 0.27 times) ($P < 0.05$). For subgroup analyses in combined group, there were no statistical significances between rhIFN α 1b + acupuncture only group and rhIFN α 1b + acupuncture + oral immune modulator group, as well as between rhIFN α 1b + acupuncture only group and rhIFN α 1b + acupuncture + imiquimod group. For subgroup analyses in rhIFN α 1b subgroups, no statistical significances were seen between rhIFN α 1b only group and rhIFN α 1b + immune modulator group, as well as between rhIFN α 1b only group and rhIFN α 1b + imiquimod group ($P > 0.05$).

For patients with 6–9 lesions, less sessions in combined group (6.73 ± 3.70 times) were needed than those in rhIFN α 1b group (9.44 ± 4.95 times, $P < 0.05$). There were no statistical significances between combined subgroups (rhIFN α 1b + acupuncture only group vs. rhIFN α 1b + acupuncture + immune modulator group, rhIFN α 1b + acupuncture only group vs. rhIFN α 1b + acupuncture + imiquimod group), as well as rhIFN α 1b subgroups (rhIFN α 1b only group vs. rhIFN α 1b + immune modulator, rhIFN α 1b only group vs. rhIFN α 1b + imiquimod group) ($P > 0.05$).

For patients with more than ten lesions, there was no statistical difference in sessions between combined group (10.67 ± 4.52 times) and rhIFN α 1b group (10.87 ± 3.48 times) ($P > 0.05$). There were no statistical significances between combined subgroups (rhIFN α 1b + acupuncture only group vs. rhIFN α 1b + acupuncture + immune modulator group, rhIFN α 1b + acupuncture only group vs. rhIFN α 1b + acupuncture + imiquimod group), so did rhIFN α 1b subgroups (rhIFN α 1b only group vs. rhIFN α 1b + imiquimod group) ($P > 0.05$) (Table 2).

Adverse effects

All of the patients complained of varying degrees of pain in local injection or laser ablation. More patients in combined group (75.03%, 697/929) and rhIFN α 1b group (75.65%, 351/464) suffered from mild fever than those in CO₂ laser

group (0%, 740) ($P < 0.05$). The fever recovered in 1 or 2 days without any treatment. Less patients in combined group complained of swelling (13.02%, 121/929 vs. 100%, 740/740) and scar (1.61%, 15/929 vs. 22.97%, 170/740) than those of CO₂ laser group ($P < 0.05$). No statistical differences were found in hyperpigmentation and infection between combined group and control groups. The recovery time of CO₂ laser lasted for 2 weeks.

Recurrence rate

The recurrence rates at 3 months after the last treatment were 14.17% (121/854), 17.01% (85/498), and 25.89% (145/560) in combined group, rhIFN α 1b group, and CO₂ laser group, separately.

Discussion

In the present study, we first applied combined therapy of intralesional rhIFN α 1b injection and local acupuncture on verruca vulgaris, and got excited efficacy. For single lesion, the sessions varied according to the size of the lesions. The sessions between combined group and rhIFN α 1b group were comparable if the lesion was small, whereas the sessions of combined group were less than those of rhIFN α 1b group if the lesion diameter was bigger than 6 mm. The results illustrated that intralesional rhIFN α 1b injection was a good modality for small single verruca vulgaris, and additional local acupuncture decreased sessions for medium and big lesions. Less sessions represented more convenient and easier to be accepted by the patients. For plural lesions, sessions increased according to the number of the lesions. When there were 6–9 lesions, the sessions of the combined group were less than those of rhIFN α 1b group. But no statistical differences were found between the combined group and rhIFN α 1b group with two to five or more than ten lesions. Traditional modalities, such as cryosurgery, electrodesiccation, bleomycin, 5-fluorouracil, and surgical excision, were applied on all lesions, but acupuncture in the present study was applied on the biggest one or two lesions, indicating a simpler modality for the present combined therapy.

As shown in the present study, the cure rates and side effects (swelling and scar) of both rhIFN α 1b + acupuncture group and rhIFN α 1b group were lower than those of CO₂ group. Therefore, the combined therapy might be accepted by more young female patients because of cosmetic reasons. Moreover, the cure rate of rhIFN α 1b + acupuncture group was a little lower than that of rhIFN α 1b group, but additional local acupuncture decreased sessions of medium and big lesions. The recurrence rate after 3 months in combined group and rhIFN α 1b group was lower than that in CO₂ laser group, indicating that the combined therapy of

rhIFN α 1b and acupuncture was an alternative therapy for verruca vulgaris.

In the past, oral immune modulator and topical imiquimod were considered as traditional modalities for verruca vulgaris. However, the modalities cost such a long time and were inconvenient for patients. Some of the patients gave up because of the troublesome procedure. In our study, the combined therapy was applied at an interval of 7–10 days in hospital, which improved the compliances of patients. Moreover, oral immune modulator and local imiquimod did not reduce the sessions of the combined therapy or rhIFN α 1b under most conditions, illustrating limited efficacies of oral immune modulators and local imiquimod on verruca vulgaris.

Some potential mechanisms might participate in the combined therapy. First, verruca vulgaris is infected by HPV, which infects keratinocytes and induces minimal inflammation without lysing infected cells. Moreover, HPV decreases the maturation and antigen presentation function of the antigen presenting immune cells (Langerhans cells) [19], inhibits Type I IFN signaling pathway and results in the transcription of IFN-stimulated genes with the function of anti-virus [20]. IFN induces the production of anti-viral proteins against viral protein translation and transcription, regulates immune function by TH1 and macrophage/natural killer cell, increases antigen expression of HPV on infected cells, changes the fluidity of cell membrane by decreasing viral replication and inhibits differentiation of HPV-infected cells by decreasing HPV reproduction rate [21]. rhIFN α 1b is a human original regulatory cytokine of Type I IFN family with excellent anti-viral activity, anti-proliferation, and immunomodulation [22]. It eliminates virus by blocking viral replication and enhancing innate immune response [23]. Second, intralesional acupuncture blocks the microcirculation at the bottom of the warts, thus induces shrinkage of the lesions. The combined therapy acuminates eliminating of the warts.

Conclusion

The combined therapy of local applied rhIFN α 1b and acupuncture was beneficial for verruca vulgaris. However, there were some limitations. First, the retrospective study was only from one hospital, that random clinical trials (RCTs) from multiple centers would be more persuasive. Second, no long follow-up was reported in the present study; thus, the recurrence rate was incomparable. Therefore, more RCTs with long follow-up should be taken in the future to confirm the results.

Author contributions LiangHong Chen, BiHuan Xiao and JingYu Wang wrote the main manuscript text, Yan Wu, Yan Sun and XingHua Gao edited the manuscript, Shuai Qiao and Qian An prepared figures 1-4. All authors reviewed and approved the manuscript.

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Declarations

Conflict of interest The authors declare that he they have no competing interests.

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