Original Article

A Study of Comparison and Evaluation of Various Intralesional Therapies in Cutaneous Warts

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Abstract

Background: The study compares the efficacy of four immunotherapeutic agents, measles mumps and rubella (MMR), purified protein derivative (PPD), *Candida* extract, and vitamin D3, in the treatment of multiple cutaneous warts. **Aim and Objectives:** To observe the clinical responses and safety of different intralesional immunotherapeutic agents and compare their efficacy. **Materials and Methods:** Hundred patients with multiple (>5) cutaneous warts were enrolled in the study and randomized into four groups: Group A: MMR, Group B: PPD, Group C: *Candida* extract, and Group D: Vitamin D. Target wart was selected, and the intralesional injections were given at three weekly intervals for a maximum of three doses. Response was observed in target and distant warts three months after the last injection. **Results:** Intralesional vitamin D3 had the highest efficacy, while MMR had the lowest efficacy in clearance of target wart. Intralesional *Candida* extract had the highest efficacy, while vitamin D3 had the lowest efficacy in clearance of distant warts. Intralesional *Candida extract* was the most effective treatment for both local and distant warts. Side effects were minimal and transitory in nature. **Conclusion:** Intralesional immunotherapy is a safe, affordable, and efficacious treatment for warts.

Keywords: *Cutaneous warts, intralesional immunotherapy, intralesional vitamin D3*

Introduction

Warts or verrucae are the benign proliferations of skin and mucosa caused by infection with the human papilloma virus (HPV).

Various treatment modalities for warts include reassurance, local destructive therapies, surgical therapies, virucidal agents, antiproliferative agents, occlusotherapy, topical immunologic therapy such as imiquimod, contact immunotherapy with diphencyprone (DPC) or squaric acid dibutyl ester (SADBE), and intralesional immunotherapy with *Candida extract*, measles mumps and rubella (MMR) vaccine, tuberculin (also known as purified protein derivative (PPD)), *Trichophyton* antigens, and vitamin D3.[1]

Systemic agents that may be used for warts include zinc oxide and zinc sulphate, histamine receptor 2 antagonists, and isotretinoin.

Among all these available modalities, no single treatment is uniformly effective or virucidal, and failures and recurrences are common. Different types of warts may need different site-dependent treatments, and sometimes different modalities may need to be combined. Because of the cumbersome nature of destructive procedures and associated high risk of recurrence, immunotherapy is becoming more and more popular, especially in the treatment of refractory warts.[2,3]

In this study, we attempt to compare four modalities of intralesional immunogens - intralesional MMR, PPD, *Candida extract*, and vitamin D3, for which no studies are available.

Materials and Methods

An open-label, randomized, prospective, interventional study was conducted in the outpatient department of dermatology, venereology, and leprosy at a tertiary care center over a period of 2 years (August 2019 to August 2021) after the approval of the NHL institutional review board dated August 29, 2019, numbered NHLIRB/2019/AUGUST/29/no. 1. Sample size calculation

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was done by taking the proportions, 0.846 and 0.40, based on the study done by Nofal *et al*.[4] and Kareem *et al*.[5] for a power of 90% and 5% levels of significance. Thus, the required sample size was 23 patients per group, adding up to a total of 92 patients. By considering the 10% drop out rate, the total number of patients required was 102. Patients with multiple (>5) cutaneous warts aged between 18 and 75 years who had not been previously treated with any other modality, and who gave consent were selected. Pregnant and lactating females, immunosuppressed patients, and patients with warts limited to face and genitals were excluded.

Written informed consent was taken, and detailed history including the demographic data (age, sex, occupation, marital status) and history regarding warts (onset of the lesions, duration of the lesions, any prior treatment) were noted. The photographs were taken using a digital camera, and the same camera was used throughout the study. Confidentiality of all records was maintained. All the baseline investigations and serum human immune deficiency virus (HIV), hepatitis B surface antigen (HbsAg), Mantoux test, and chest X-ray were done. All the patients with cutaneous warts were divided into the four treatment groups with simple random sampling using envelopes prepared with the help of sealed envelope.com website (computer generated). We made four envelopes, each containing 25 envelopes of Groups A, B, C, and D with allocation ratio of 1:1. The detailed methodology is explained in Figure 1.

Target wart was defined as the largest wart in which immunogen was injected. In cases where the size of the target wart decreased significantly in between the sessions, the largest wart from remaining lesions was considered as the target wart for that session.

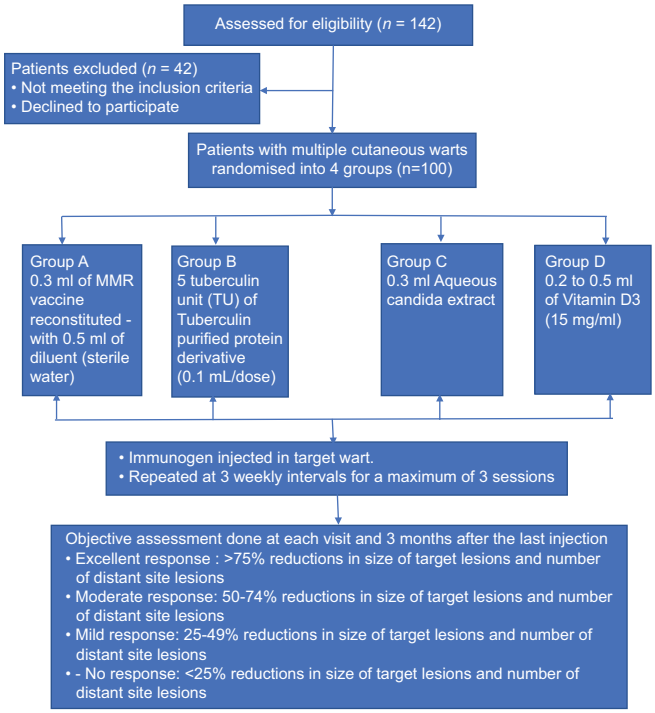

Figure 1: Methodology of study

Distant site was defined arbitrarily as un-injected wart that was away from the target wart.[6,7]

All the patients were evaluated for treatment efficacy, recurrence, and any adverse reactions. Treatment efficacy was defined as excellent response being >75% reduction in size of target lesion and number of distant site lesions, moderate response being 50–74% reduction in size of target lesion and number of distant site lesions, mild response being 25–49% reduction in size of target lesion and number of distant site lesions, and no response being <25% reduction in size of target lesion and number of distant site lesions.

Follow-up was done after three months of the last dose of injectable. Results were analyzed using Cochran's Q test.

Results

A total of 100 patients enrolled were equally divided into four groups by randomization. Out of which, 58% were male patients and 42% were female patients. The most common location of warts was acral. A total of 53% of the patients had a disease duration of fewer than six months. Only 2% of the patients had a positive family history. Eighty-eight percent of the patients had target warts less than 30 mm^2.

Efficacy: Efficacy on the 21st day and the 63rd day of study of all four groups has been summarized in Table 1.

Efficacy at three months after the last injection: After the completion of the study, that is at three months after the last injection, in treatment Group A, 68% had complete clearance at the local site and 60% had complete clearance at the distant site. In treatment Group B, 84% had complete clearance at the local site and 72% had complete clearance at the distant site. In treatment Group C, 84% had complete clearance at the local site and 80% had complete clearance at the distant site. In treatment Group D, 100% had complete clearance at the local site and 0% had complete clearance at the distant site [Table 2 and Figures 2-6].

On comparing results, *P* value for Group A vs Group B was 0.9517, Group B vs Group C was 0.9911, Group A vs Group C was 0.8715, Group A vs Group D was 0.001, Group B vs Group D was 0.001, and Group C vs Group D was 0.001. There were statistically significant differences in overall response between vitamin D3 and other immunotherapeutic agents in warts. Eight patients who showed no response in Group A [Figure 7] at the end of the study were treated with other alternative modalities.

Safety: In treatment Group A, there were no side effects in patients. In treatment Group B, one patient had mild swelling with erythema at the local site after a day of intralesional injection which subsided in four days and one patient had

Table 1: Efficacy observation in study patients after first and third sessions

Group	After first session (21st day)				After third session (63rd day)			
	Mild *n*(%)*	Mod *n*(%)**	Excellent *n*(%)***	No *n*(%)#	Mild *n*(%)*	Mod *n*(%)**	Excellent *n*(%)***	No *n*(%)#
Group A	14	2	0	9	6	3	14	2
	(56%)	(8%)	(0%)	(36%)	(24%)	(12%)	(56%)	(8%)
Group B	22	0	0	3	1	2	19	3
	(88%)	(0%)	(0%)	(12%)	(4%)	(8%)	(76%)	(12%)
Group C	22	1	0	2	1	0	21	3
	(88%)	(4%)	(0%)	(8%)	(4%)	(0%)	(84%)	(12%)
Group D	25	0	0	0	25	0	0	0
	(100%)	(0%)	(0%)	(0%)	(100%)	(0%)	(0%)	(0%)

***Excellent response: >75% reduction in size of target lesion and number of distant site lesions. **Moderate response: 50–74% reduction in size of target lesion and number of distant site lesions. *Mild response: 25–49% reduction in size of target lesion and number of distant site lesions. #No response:<25% reduction in size of target lesion and number of distant site lesions

Table 2: Results after three months of the last session

Treatment	Complete clearance				Total
	Local site (*n*)	%	Distant site (*n*)	%	
Group A	17	68.00%	15	60.00%	25
Group B	21	84.00%	18	72.00%	25
Group C	21	84.00%	20	80.00%	25
Group D	25	100.00%	0	0.00%	25

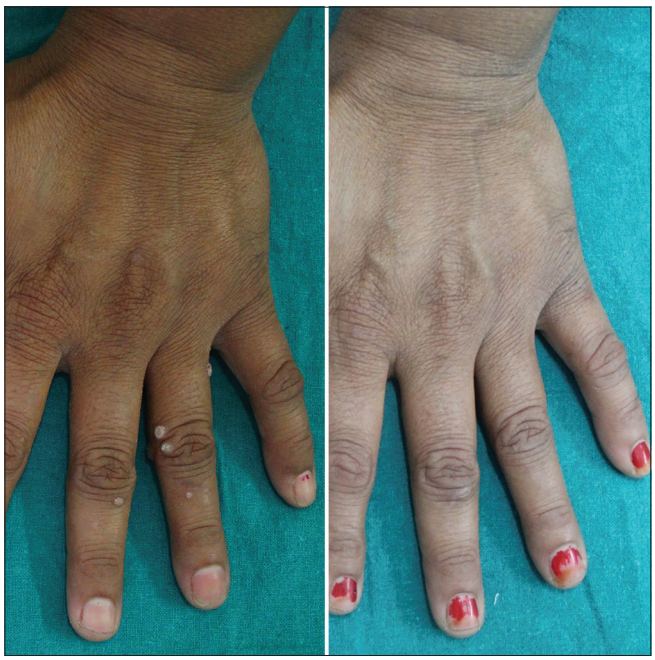

Figure 2: Excellent response in Group A both at local and distant sites

ulcers at the intralesional site after five days which healed in 15 days. In treatment Group C, one patient had swelling over the intralesional site which subsided in five days. In treatment Group D, all patients had pain while giving injection and two patients had swelling at the local site [Table 3].

Discussion

Warts do regress spontaneously, but can persist for a long duration and cause physical discomfort and psychological trauma.[8] Relapse with the development of new lesions can occur due to the failure of the immune system to detect and remove the HPV virus. Treatment of warts should be effective with the least chances of recurrence and side effects.[9] There are multiple treatment modalities available that aim at local destruction and/or induction of the host immune system. The destructive treatments used for warts may not stimulate the host immunity, and if warts are not destroyed properly, the remaining infective tissue may lead to recurrence.[10] The destructive treatments, such as electrocauterization and carbon dioxide laser, are painful and may leave scars. Autoinoculation may lead to the induction of cell-mediated immunity and affect local and distant warts.[11] The various intralesional therapies with various antigens (MMR, PPD, BCG, *Mycobacterium w* vaccine, *Candida* antigen, vitamin D3, and bleomycin) lead to induction of cell-mediated immunity and affect local and distant warts, and are more useful in the cases of large and multiple warts.[3] The exact mechanism by which intralesional immunotherapy works is still not clear. It is proposed that production of Th1 cytokines, TNF-α, and INF-γ, downregulates the transcription of HPV genes and stimulates cytotoxic T cells and natural killer cells to eradicate HPV-infected cells.[12] This study aimed to evaluate the efficacy and safety of various modalities of intralesional therapy for the treatment of multiple cutaneous warts.

In the present study, 58 patients were males and 42 patients were females, with a male-to-female ratio of 1.4:1. The studies of Rehna *et al*.[13] and Agrawal *et al*.[14] had male-to-female ratios of 1:1.64 and 1.7:1, respectively. The higher male prevalence may be explained by more outdoor activities among males than females.

In the study done by Rehna *et al*.,[13] a greater number of patients had a mean duration of warts of 1 year, and in the study done by Shaheen *et al*.,[15] it was 6.5 ± 3 months. Maximum patients (53%) had warts for one to five months in our study.

In our study, we had compared four intralesional treatment modalities - MMR, PPD, *Candida* antigen, and vitamin

Table 3: Adverse effects

Group	Side effects						Total
	Mild swelling and erythema	Swelling	Pain	Pain and swelling	Ulcers	No	
Group A	0	0	0	0	0	25	25
Group B	1	0	0	0	1	23	25
Group C	0	1	0	0	0	24	25
Group D	0	0	23	2	0	0	25
Total	1	1	23	2	1	72	100

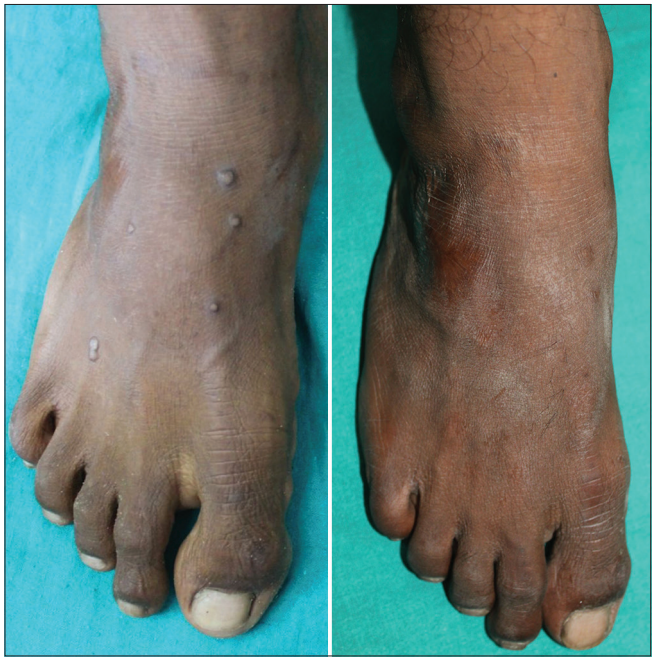

Figure 3: Excellent response in Group B both at local and distant sites

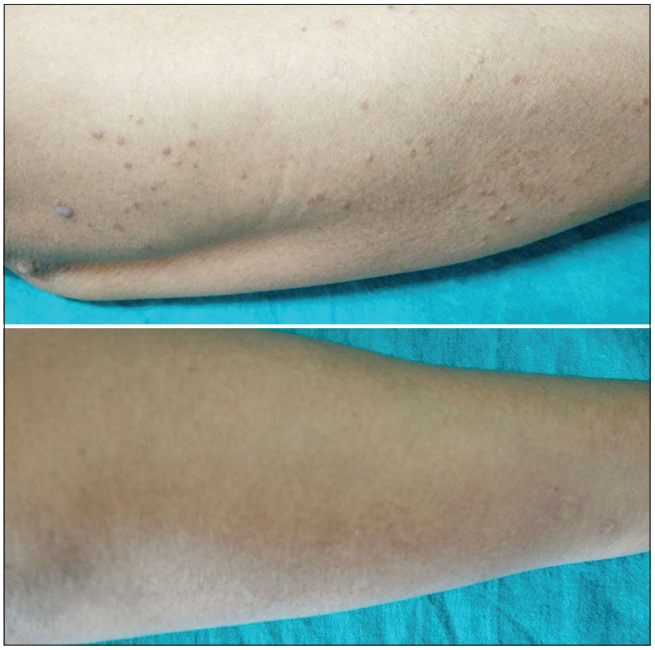

Figure 4: Excellent response in Group C both at local and distant sites

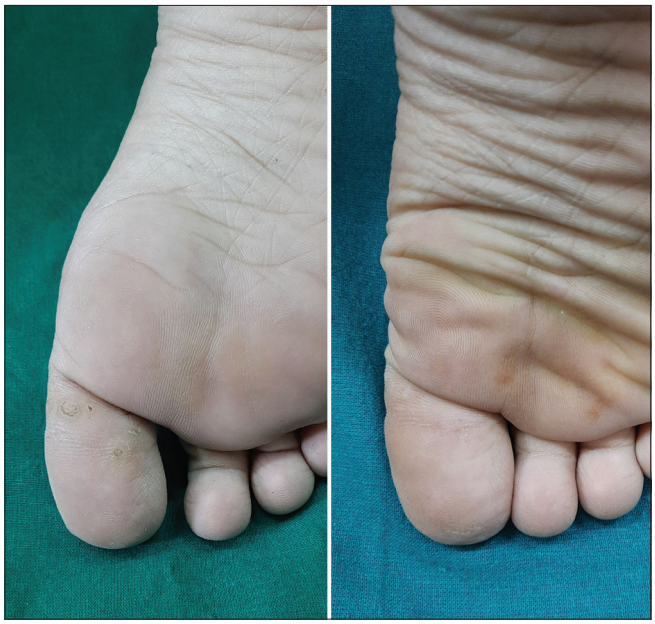

Figure 5: Excellent response in Group D at local site

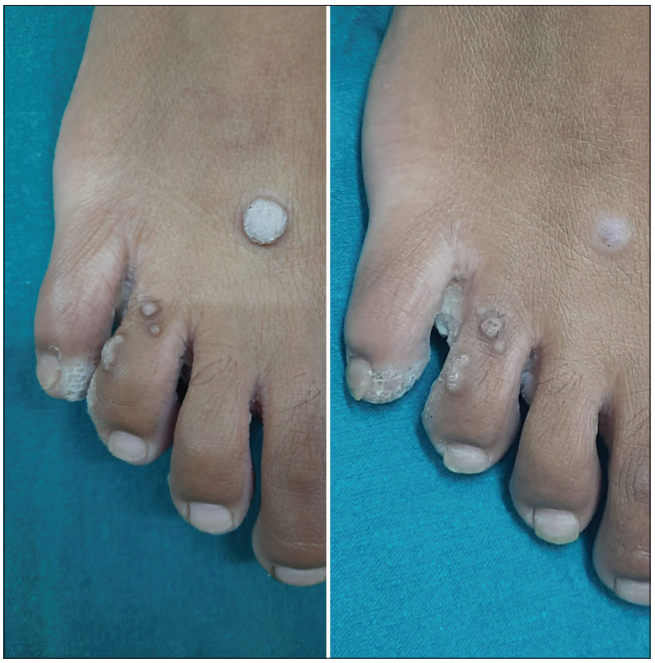

Figure 6: No response in Group D at distant site

D3 injections, out of which intralesional vitamin D3 had 100% efficacy (clearance) at the local site followed by intralesional *Candida* (84%), intralesional PPD (84%), and intralesional MMR (68%). Maximum clearance

Table 4: Comparison of therapeutic response and adverse reactions with other studies

Therapeutic agent	Response	Comparison					
		Our study (*n*=25)		Shaheen *et al*.[15] (*n*=10)		Agrawal *et al*.[14] (*n*=30)	
MMR		**Local site**	**Distal site**	**Local site**	**Distal site**	**Local site**	**Distal site**
	Complete clearance	68% (17)	60% (15)	80% (8)	40% (4)	60% (18)	53.3% (16)
	Side effects	No side effects		Erythema, swelling, and vasovagal attack - 10%		Pain – 60% (18) Erythema – 13.3% (4)	
PPD		**Our study (*n*=25)**		**Shaheen *et al*.[15] (*n*=10)**			
		Local site	**Distal site**	**Local site**		**Local site**	
	Complete clearance	84% (21)	72% (18)	80% (8)		80% (8)	
	Side effects	Swelling, erythema, and local site ulceration – 8% (2)		No side effects			
***Candida* extract**		**Our study (*n*=25)**		**Lamis *et al*.[18] (*n*=30)**			
		Local site	**Distal site**	**Local site**		**Distal site**	
	Complete clearance	84% (21)	80% (20)	76.7% (23)		23.33% (7)	
	Side effects	Swelling - 1% (1)		Swelling – 23.3% Erythema and tenderness – 26.7%			
Vitamin D3		**Our study (*n*=25)**		**Lamis *et al*.[18] (*n*=30)**			
		Local site	**Distal site**	**Local site**		**Distal site**	
	Complete clearance	100% (25)	00% (00)	20% (6)		6.66% (2)	
	Side effects	Pain – 100% (25) Pain and Swelling – 8% (2)		Swelling – 20% Erythema and tenderness – 20% Minimal tolerable pain - 100% Vasovagal attack - 1 patient			

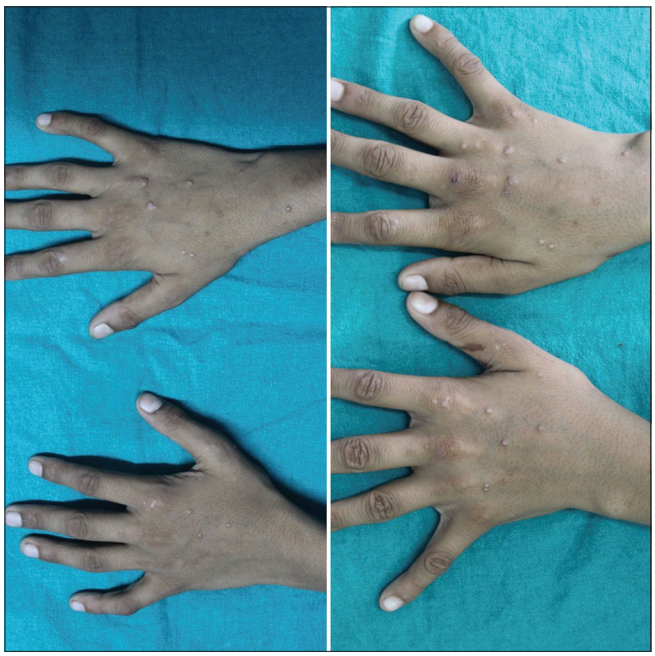

Figure 7: No response in Group A at local site

of warts at the local site with intralesional vitamin D3 may be due to its additional effect of normalizing the increased rate of keratinocyte proliferation at a higher concentration.[16]

While on distant sites, the efficacy of intralesional *Candida extract* (80%) was superior to intralesional PPD (72%), followed by intralesional MMR (60%). However, no improvement was seen in the distant lesions in patients treated with intralesional vitamin D3 injection. No resolution at the distant sites with intralesional vitamin D3 may be due to its less antigenicity compared to other agents. Clearance of warts at the distal sites was maximum with *Candida* extract followed by PPD and MMR, which may be due to the antigenicity and maximum induction and stimulation of CMI.

Intralesional vitamin D3 was the most effective in local cutaneous warts with minimal side effects. Intralesional *Candida* antigen was the most effective at local and distant sites with minimal side effects.

There was inter-individual variation in response to immunotherapeutic agents. That might be because of differences in immunity among different people, differences in the serotype of infecting HPV virus, and severity of infection. Availability of medication and cost of treatment are some limitations that need to be addressed.[17]

Comparison of the percentage of complete clearance of warts at local and distal sites and adverse effects with different studies is mentioned in Table 4.[14,15,18]

Study limitation

Exclusion of patients of age less than 18 years, limited sample size, and short period of follow-up are some limitations of the study. Our study could not identify HPV types to account for type-specific differences in therapy.

Conclusion

Intralesional immunotherapies are safe, affordable, well-tolerated, and efficacious treatments for warts.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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