



JOURNAL OF ZANKOY SULAIMANI

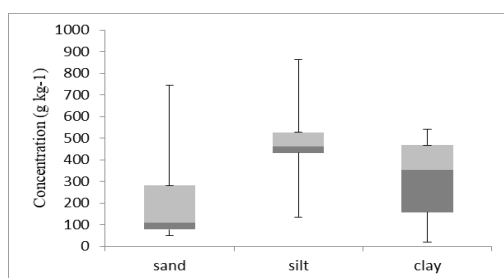
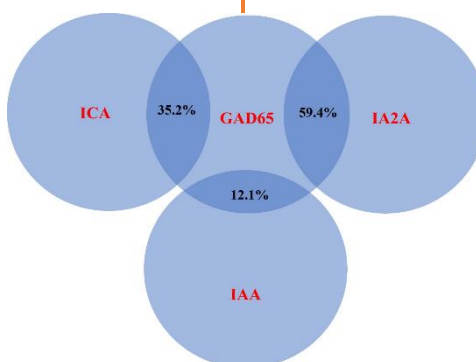
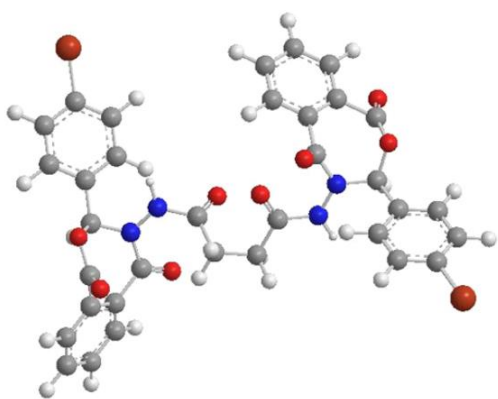
Part -A- (Pure and Applied Sciences)

VOLUME 25 ISSUE 2 December 2023

ISSN: 1812-4100

www.jzs.univsul.edu.iq

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Efficacy and Safety of Oral Propranolol for Facial Flushing and Erythema of Rosacea Compare to Doxycycline, Sulaimaniyah, Iraq

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Article info

Original: 10/04/2023
Revised: 18/05/2023
Accepted: 20/05/2023
Published online:
20/12/2023

Keywords:

*Rosacea, erythema,
flushing, propranolol,
doxycycline,
interventional study*

Abstract

Background: Rosacea is an inflammatory skin disease characterized by erythema and flushing, where topical medications are challenging to control and treat. **Objectives:** To investigate the effect of systemic propranolol/doxycycline in treating facial flushing and erythema in patients with rosacea. **Patients and Methods:** This randomized control trial study was conducted on 51 patients with rosacea referred to the Sulaimani Dermatology Teaching Center, Sulaimaniyah, Iraq, from October 2021 to August 2022. Among the studied patients, 31 patients were taking oral propranolol, 28 of them did finish the course, while 20 patients were treated with oral doxycycline, 18 of them finished the treatment. Patients have been seen in 5 sessions (12-week treatments), and in each session, the patient's health status, the recovery process of the disease and vital signs have been checked and recorded. **Results:** The mean age of patients age was 46.65 ± 10.38 years. Most patients were females (65.2%), did not take any drugs (78.4%), did not have a history of illness in the family (82.6%), had skin type 2, and had flushing distribution in the forehead, nose, cheek, and chin. The most common symptom in patients was a burning sensation, followed by a burning and tingling sensation. The most common sign in both groups was erythema. Propranolol positively affected clinical erythema assessment, area, telangiectasia, total erythema score, systolic/diastolic blood pressure and heart rate. Thus, in 5 visits, erythema was significantly reduced in the propranolol group compared to the doxycycline group ($p \leq 0.002$). So that after the 5 visits the CAT score was shown that erythema was significantly reduced in the propranolol group compared to the doxycycline group ($p \leq 0.001$). **Conclusions:** Propranolol was more effective than doxycycline in the treatment of rosacea's flushing and erythema.

Introduction

Rosacea is a chronic inflammatory skin condition with multifactorial pathophysiology that primarily affects the center of the face [1]. Rosacea affects more than 15 million Americans and is associated with significant emotional, physical, and financial costs [2]. It can occur at any age; however, the average beginning is after age 30 [3].

The condition progresses typically between remissions and exacerbations, affecting up to 10% of fair-skinned people. However, the state is not restricted to fair skin; it can also be found in the colored skin [4]. The disease's clinical manifestations include papules, pustules, edema, telangiectasia, and facial erythema (permanent or temporary). One of these symptoms may be present, or a mixture of them. Patients may not exhibit symptoms

or express burning, stinging discomfort, or pruritus [4, 5]. Symptoms may begin with flushing and progress to enduring erythema [6]. The most common presenting sign in all subtypes of rosacea patients is transient or persistent facial erythema [7] that often affects the middle of the face and has a diffuse pattern of distribution [8].

Current rosacea therapy options include topical metronidazole, topical azelaic acid, and systemic tetracycline, focusing more on inflammatory alterations than erythema. Although topical metronidazole/azelaic acid theoretically cures erythema on a molecular level, recent studies reveal these frequently fail to do so, mainly if the condition has grown chronic [8]. In addition, limited topical medications successfully treat diffuse face erythema in rosacea patients. Topical steroids are quite popularly utilized; however, cutaneous atrophy and flare-ups are unavoidable and become visible after the medication is stopped. For those reasons, rosacea sufferers should refrain from using topical corticosteroids [7, 9].

In order to treat refractory face erythema, β -blockers might be utilized. The nonselective β -adrenergic antagonist nadolol and propranolol work well to lessen flushing. However, they might not be used as often because of their potential adverse effects, such as bradycardia and hypotension [10]. Nonselective β -blockers are believed to reduce the erythema and flushing associated with rosacea by blocking β -adrenergic receptors on the smooth muscles surrounding blood vessels, which causes the vessels to contract [11]. In addition, these drugs may help reduce tachycardia and anxiety, the leading causes of worsening flushing episodes [10].

There are only a few reports of β -blocker therapy in patients with rosacea, and there are only a handful of studies on the effectiveness of propranolol in rosacea. Therefore, this study aimed to investigate the effect of systemic propranolol in treating facial flushing and erythema in rosacea patients compared to doxycycline treatment.

Materials and Methods

Study design

This randomized control trial (RTC) study was conducted on 51 patients with rosacea who were referred to Sulaimani Dermatology Teaching Center, Iraq, from October 12 2021, to August 07 2022.

Study setting

Initially, clinical erythema assessment (CEA) score and telangiectasia were done for all patients [12], and they were divided into 2 groups. Case group is to be treated with systemic propranolol (no.=31), and control group is to be treated with doxycycline (no.=20). In addition, patients' age, gender, history of chronic medication, family history of rosacea, history of allergies, blood pressure and heart rate were recorded using a well-designed questionnaire, while patients with bradycardia had electrocardiography (ECG).

Inclusion criteria

Patients with rosacea aged >18 years.

Exclusion criteria

Patients with severe side effects and hypersensitivity to previous treatments and drug interaction, those with psoriasis, asthma, hypotension, bradycardia, pregnancy, hypoglycemia, and congestive heart failure were excluded. Also, patients that received propranolol treatment previously were not included.

Ethical consideration

This study protocol was approved by the scientific and ethical committee of the College of Medicine, University of Sulaimani, Sulaimaniyah, Iraq (No. 220 on November 07-2021). All methods and procedures followed the basic principles of the Declaration of Helsinki. In addition, written informed consent was obtained from all patients, and the study's objectives were explained to the patients.

Study procedure

Patients in case group received 10 mg of oral propranolol thrice daily on the first visit. Whereas in the subsequent visits, the drug dosage was prescribed up to 40 mg twice a day according to the patient's signs and symptoms and their vital signs. For patients in control group, 100 mg of oral doxycycline was prescribed once daily.

In 5 visits, the patient's lesions and skin health were examined clinically and by dermoscopy. In case of any problems or side effects, the treatment was carried out in a timely manner. Patients' CAT score which is (CEA, area, telangiectasia), vital signs (systolic and diastolic blood pressure and pulse rate), and clinical symptoms were recorded during each visit. Patients were followed-up at 2, 4, 8 and 12 weeks' intervals.

The CEA score has a 5-point scale (0-4) to measure the severity of erythema (Supplementary 1), the area score consists of 3-point values using the palm method to measure the extent of erythema on the face (Supplementary 2) and the telangiectasia severity score to measure telangiectasia on a 3-point scale (Supplementary 3).

Data analysis

Data analysis was done using IBM SPSS, version 23. The descriptive statistics section reported frequency and frequency percentage for qualitative variables, and mean ± standard deviation (SD) was reported for quantitative variables. Friedman test was used to investigate the effects of propranolol on the clinical condition of patients, blood pressure and heart rate. The P-value was set as highly significant ($p \leq 0.001$), effective ($p \leq 0.05$), non-significant ($p \geq 0.05$), and very highly significant ($p \leq 0.000$).

Results

Regarding the patients' sociodemographic characteristics, the mean±SD of age was 46.65±10.38 years. Most patients were females (65.2%), not on chronic medication (78.4%), and without a family history of rosacea (82.6%) (Table 1). The mean age in the propranolol treatment group was 47.86±10.248 years, while in the doxycycline treatment group was 44.78±10.60 years ($p=0.716$). Most patients in the propranolol treatment group (64.3%) were females, had skin type 3 (42.9%), were not on chronic medication (71.45%), and had flushing on the forehead, nose, cheek, and chin (53.6%). Similarly, most patients on doxycycline treatment were females (66.7%), had skin type 3 (38.9%), were not on chronic medication (88.9%), and had flushing on the forehead, nose, cheek, and chin (38.9%). There were no significant differences between both groups ($p \geq 0.05$) (Table 2).

Table 1: Baseline characteristics of studied participants.

Variable	Frequency	Percentage
Age (mean±SD)	46.65±10.38	
Gender		
Male	16	34.8
Female	30	65.2
Chronic drug use		
Yes	10	21.7
No	36	78.3
Used drugs		
Systemic	5	10.9
Topical	5	10.9
No drug use	36	78.3
Family history		
Yes	8	17.8
No	38	82.6
Total	46	100

Table 2: Distribution of characteristics in case and control groups.

Variable	Case group	Control group	P-value*
	Number, %		
Gender			
Male	10 (35.7)	6 (33.3)	0.869
Female	18 (64.3)	12 (66.7)	
Skin types			
Type 2	9 (32.1)	5 (27.8)	0.827
Type 3	12 (42.9)	7 (38.9)	
Type 4	7 (25)	6 (33.3)	
Chronic drug use			
Yes	8 (28.6)	2 (11.1)	0.161
No	20 (71.4)	16 (88.9)	
Type of used drug(s)			
Systemic drug	5 (17.9)	0 (0)	0.162
Topical drug	3 (10.7)	2 (11.1)	
No drug use	20 (71.4)	16 (88.9)	
Distribution of flushing			
Forehead, nose, cheek, chin	15 (53.6)	7 (38.9)	0.329
Forehead, nose, cheek	6 (21.4)	6 (33.3)	
Nose, cheek	4 (14.3)	2 (11.1)	
Nose, cheek, chin	1 (3.6)	3 (16.7)	
Forehead, cheek	2 (7.1)	0 (0)	

*P-value was calculated using Independent t test (only for gender) and Chi-square test.

The most common symptoms of the rosacea in case group were burning sensation (17.9%), followed by burning and stinging or severe pruritus (14.3%), then stinging, or pruritus (10.7%), and the least had burning sensation/stinging (7.1%), while 25% showed no symptoms of the disease. The most common symptom in the control group was a burning sensation (27.8%). In comparison, stinging/pruritus were seen in 16.7% of patients, followed by burning and stinging (11.1%), stinging and pruritus (5.6%), and with no burning and pruritus sensation. While 22.2% of patients declared had no symptoms. Both groups had no significant difference in terms of disease symptoms ($p \geq 0.05$) (Table 3).

Table 3: Distribution of the rosacea medical presentation in studied patients.

Variable	Case group	Control group	P-value
	Frequency n=28	Frequency n=18	
Symptoms			
Burning sensation	5 (17.9)	5 (27.8)	0.587
Stinging	3 (10.7)	3 (16.7)	
Pruritus	3 (10.7)	3 (16.7)	
Burning sensation + stinging	2 (7.1)	2 (11.1)	
Burning sensation + pruritus	4 (14.3)	0 (0)	
Stinging + pruritus	4 (14.3)	1 (5.6)	
None	7 (25)	4 (22.2)	
Duration of symptom (Year)			
≤1	14 (50)	3 (16.7)	0.145
2 – 4	7 (25)	7 (38.9)	
5 - 10	5 (17.9)	5 (27.8)	
>10	2 (7.1)	3 (16.7)	
Aggravating factors			
More than one factor	16 (57.1)	9 (50)	0.898
Sun exposure	6 (21.4)	6 (33.3)	
Hot drink	2 (7.1)	1 (5.6)	
Spicy food	1 (3.6)	0 (0)	

Cold exposure	1 (3.6)	1 (5.6)	
Stress	1 (3.6)	1 (5.6)	
Alcohol ingestion	1 (3.6)	0 (0)	
Sign			
Erythema	13 (46.4)	5 (27.8)	0.002*
Papule	0 (0)	5 (27.8)	
Pustule	0 (0)	4 (22.2)	
Erythema + Papule	9 (32.1)	4 (22.2)	
Erythema + Pustule	1 (3.6)	0 (0)	
Erythema + Papule + Pustule	5 (17.9)	0 (0)	
Dermoscopic features			
Group8 -Polygonal network, arborizing vessels (V), linear V	8 (28.6)	5 (28)	0.969
Group2 -Polygonal network, arborizing V, linear V, follicle plug	5 (17.9)	2 (11.1)	
Group9 -Linear V, arborizing V	4 (14.3)	1 (5.5)	
Group3 -Polygonal network, arborizing V, linear V, follicle plug, follicle opening	3 (10.8)	3 (16.9)	
Group4 -Linear V, follicle plug, arborizing V	2 (7.2)	1 (5.5)	
Group10 -Polygonal network, arborizing V, linear V, follicle plug, superficial scales	2(7.2)	1 (5.5)	
Group1 -Polygonal network, linear V, follicle plug, follicle opening	1 (3.5)	1 (5.5)	
Group6 -Polygonal network, arborizing V, linear V, follicle plug, follicle opening, superficial scales	1(3.5)	1 (5.5)	
Group7 -Linear V, follicle plug, follicle opening, superficial scales	1(3.5)	1(5.5)	
Group11 -Polygonal network, arborizing V, linear V, follicle opening, superficial scales	1(3.5)	1 (5.5)	
Group5 -Arborizing V, follicle plug	0(0)	1 (5.5)	

*: Significant difference using Chi-square test

Regarding the duration of symptoms, most patients (50%) patients in case group had a history of symptoms for ≤ 1 year, while most patients (38.9%) in control group had a history of symptoms for 2-4 years. Concerning the disease-aggravating factors, most patients in case group (57.1%) and control group (50%) had more than one disease-aggravating factor. Regarding the sign of the disease, erythema was commonly found in case group (46.4%), while erythema and papule were most commonly found in control group (27.8%). Both groups were significantly different regarding signs ($p \leq 0.002$). Additionally, the widely seen dermoscopic features in both groups were polygonal networks, arborizing vessels and linear vessels (28.6% in Group 1 and 28% in Group 2 patients) ($p=0.969$) (Figure 1 and Table 3).

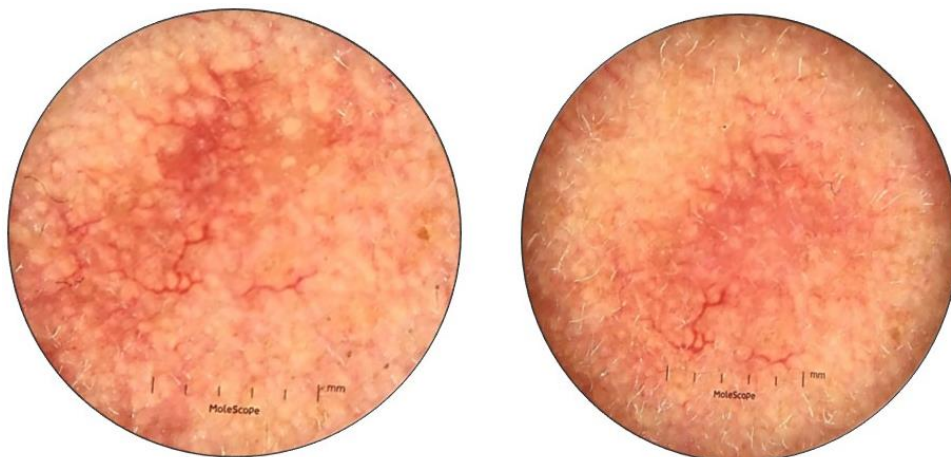


Figure 1: The dermoscopy of rosacea patient before treatment (Left side) and after oral propranolol treatment (Right side).

The results of CEA score indicated that propranolol significantly reduced patients' erythema in a total of 5 visits ($p \leq 0.001$). Similarly, the area and telangiectasia variables also decreased significantly ($p \leq 0.001$) (Figure 2). Moreover, during 5 patients' visits, it was found that systolic/diastolic blood pressure and heart rate also decreased significantly ($p \leq 0.001$), but still within the normal range (Table 4).



Figure 2: A 50-years old female with rosacea at first visit (Left side) and after 12-weeks treatment with oral propranolol (Right side).

The effect of propranolol on the condition of erythema was also investigated in both groups during five visits. In the first visit, the mean erythema in the case group was 8.0 ± 3.07 , while in control group was 6.33 ± 1.53 ($p \leq 0.001$). In the subsequent visits, the mean erythema in case group decreased more than in control group ($p \leq 0.001$) (Table 5).

Table 4: Distribution of the effects of systemic propranolol on patients' variables during all visits.

Variable	1st visit Median (IQR)	2 nd visit Median (IQR)	3 rd visit Median (IQR)	4 th visit Median (IQR)	5 th visit Median (IQR)	P-value
CEA	2(1)	2(1)	2(1)	1(1)	1(0.75)	<0.001*
Area	3(1)	3(1)	2(1)	2(1)	1(0)	<0.001*
Telangiectasia	1(1)	1(1)	1(0)	1(0)	1(0)	<0.001*
Total score	7.5(5)	7(4.5)	5(2)	3(2.75)	3(1)	<0.001*
Systolic	130(20)	120(20)	120(27.5)	110(20)	110(17.5)	<0.001*
Diastolic	80(7.5)	80(10)	80(10)	70(10)	70(20)	<0.001*
Pulse Rate	82(12)	76(9.75)	73.5(8)	70(6.75)	69.5(6.5)	<0.001*

*: Significant difference using Friedman test

Table 5: Erythema assessment score comparison between case group and control group.

Total score	Case group	Control group	P-value
	Mean±SD		
Visit 1	8.0±3.07	6.33±1.53	0.038*
Visit 2	7.11±2.79	5.44±1.69	0.028*
Visit 3	5.07±2.79	3.11±1.13	0.007*
Visit 4	3.68±1.93	2.28±0.57	0.005*
Visit 5	2.82±1.47	1.56±0.62	0.001*

*: Significant difference using Independent t test

Discussion

Classification of rosacea based on clinical symptoms might help choose treatment related to symptoms [13]. β -blockers can be effective and valuable in treating inflammation and erythema in rosacea by directly affecting vascular contraction. When conventional treatments do not affect the disease, the use of β -blockers can be promising, especially propranolol which can be very effective in treating the disease [14-16].

Thus, in this study, the effect of propranolol on the treatment of rosacea was investigated, and the results showed that the mean age of the patients was 46.65 ± 10.38 years, and most of them were women (65.2%). These findings are close to that found by Chung et al., 2022 in Korea, who found the mean age of the patients was 45 years and most of them were women [17]. While Suggs et al., 2020 found that most patients were females, however, the mean age of the patients was 51 years, which was higher than that observed in this study [18]. Similarly, Lova Navaro et al., 2018 in Spain showed that the mean age of the patients was higher than in this study, and most of the participants were women [19]. Furthermore, in this study, most patients were not on chronic medication (78.4%), which is similar to that found by Chen et al., 2021 (67.5%) [20]. On the other hand, most patients were without a family history of rosacea (82.6%). This result is inconsistent with that found by Dall'Oglio et al., 2022, who found 49.2% of patients were positive for family member with rosacea [21] and Rainer et al., 2015 who found a family history of rosacea has been observed in 50% of patients [22].

Most patients in this study had a skin type III, while Dall'Oglio et al., 2022 reported skin phototype 2 to be most frequently reported in studied patients [21]. Furthermore, examining the distribution of flushing in the examined patients showed that most of them had flushing in all parts of the forehead, nose, cheek, and chin, which was similar to that of Wienholtz et al., 2021 who showed that patients had the highest distribution of flushing in forehead, nose and cheek areas [23].

Consequently, burning sensation, stinging and pruritus were the most acute symptoms of the disease in the patients of this study, while Halioua et al., 2016 found that flushing was the most common sign of the disease, followed by telangiectasia, papules/pustules, and rhinophyma [24]. Simultaneously, Harper et al., 2018 reported lushing/flushing and bumps/pustules as the most bothersome symptoms in rosacea patients [25]. Additionally, patients were reported to have a ≤ 1 and 2-4 years' disease duration for Groups 1 and 2, respectively. In this regard, Dall'Oglio et al., 2022 reported a mean disease duration of 9.7 ± 11 years in studied patients [21], while Pekmezci, 2020 found the mean duration of the rosacea to be 102 ± 119 months [26].

Regarding the aggravating factors that exacerbate the rosacea, most patients had several aggravating factors such as sunlight, hot drinks, spicy food, exposure to cold and stress. In this respect, Lee et al., 2018 in South Korea showed that emotional problems and stress were the most critical factors aggravating the disease, while Wada-Irimada et al., 2022 in Japan stated that temperature changes and exposure to sunlight were the essential factors aggravating the condition [27, 28]. The most common dermoscopy findings in the participants were polygonal network, arborizing vessels (V), linear V, and follicle plug. In a study by Trave et al., 2021, the most common dermoscopy findings were yellow dots, vascular polygons and follicular scales [29], while yellow and red halos, vascular polygons, and follicular pustules were found by Ge et al., 2022 [30], and Stefanou et al., 2022 reported linear reticular V, follicular plugs and pustules as the most important dermoscopy findings in patients [31].

Moreover, the results showed that the CEA, area and telangiectasia were improved with the use of the drug over time, so that with more use and in the fourth and fifth visits, the effect of the drug became more apparent and reduced erythema, area and telangiectasia in patients. These outcomes agreed with Botnaru et al., 2020, who found that systemic treatment with propranolol had a better clinical effect in controlling erythema and telangiectasia in patients with erythema telangiectatic and papulopustular acne rosacea than doxycycline [32].

Since flushing and erythema are common skin symptoms in rosacea, thus; effective and efficient treatments are still an important clinical challenge in treating the disease. In this regard, a systematic review by Logger et al., 2020 investigated the efficacy of oral β -blockers for facial flushing and erythema associated with rosacea [14]. Their results agreed with this study, which confirms that propranolol effectively reduced erythema and flushing at the start of treatment and also during follow-up of patients.

Propranolol has been used for over 50 years to treat various diseases, including blood pressure. In this study, patients' systolic/diastolic blood pressure and heart rate were decreased significantly by the effect of propranolol treatment. These outcomes align with that found by Srinivasan, 2019 who showed that this drug was effective in controlling patients' blood pressure [33].

Because doxycycline is used as a first-line drug in treating rosacea, it is sometimes associated with gastrointestinal, neurological and infections. In a clinical trial by Wang et al., 2021 in China, doxycycline and hydroxychloroquine were investigated and compared for rosacea treatment. After 8 weeks of the treatment, no difference was found between the two treatment groups regarding clinical erythema. However, the erythema improvement rate was higher in the hydroxychloroquine group than in the doxycycline group, indicating the drug's better effect [34]. Their outcomes align with this study's results, as another drug rather than doxycycline works better in the treatment of rosacea.

Conclusions

The vital pathophysiological elements of the rosacea were inflammation and vascular disorders. Oral propranolol was more effective than doxycycline in the treatment of rosacea as it reduced flushing and erythema, but still, it is less effective on telangiectasia. However, treatment strategies should be tailored to individual characteristics. Limitations of the study include the prospective nature of the study, which is not possible to investigate the side effects of the drug, also absence of special center of rosacea and limited duration of study, we couldn't collect large number of cases.

Conflict of interest

The authors confirm that they are not affiliated with or involved in any organization or entity with financial interests.

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