

Original Article

Preventive application of low molecular weight heparin ameliorates peripherally inserted central catheter-related venous thrombosis

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Abstract: Objective: Peripherally inserted central catheter (PICC) is being increasingly used in critical care settings. However, PICC is associated with various complications, particularly venous thrombosis. Our aim was to observe the effects of preventive application of low molecular weight heparin on venous thrombosis in a PICC model. Methods: All rabbits were randomly divided into four groups: a control group, and low/medium/high concentration of low molecular weight heparin groups. All rabbits were injected prophylactically with normal saline or low molecular weight heparin once a day for 7 days. A PICC model was constructed. The pathologic changes of ear vein, anterior vena cava, and venous thrombosis were investigated using hematoxylin and eosin (H&E). Biochemical testing was performed including prothrombin time (PT), activated partial thromboplastin time (APTT), and thrombin time (TT). Serum D-dimer (D2D) and fibrinogen (FG) levels were detected using Enzyme-linked immunosorbent assay (ELISA). Results: X-ray results showed that the PICC model was successfully constructed. H&E results showed that preventive application of low molecular weight heparin significantly ameliorated the pathologic damage to ear vein and anterior vena cava in the PICC model. Furthermore, we found that preventive application of low molecular weight heparin inhibited venous thrombosis in the model by H&E stain. Moreover, it significantly reduced serum FG and D2D levels in PICC model. Biochemical testing results showed that PT, APTT, and TT were significantly elevated in the PICC model. Conclusion: Our findings revealed that preventive application of low molecular weight heparin significantly ameliorates venous thrombosis in a PICC model.

Keywords: Peripherally inserted central catheter, low molecular weight heparin, venous thrombosis, D-dimer, fibrinogen

Introduction

With the continuous development of medical technology, the intravenous administration route is being greatly improved. From the peripheral closed intravenous infusion method to the peripheral venous indwelling method, the pain caused by daily puncture is effectively solved, but the indwelling time is not more than 3 days [1, 2]. On the one hand, when the irritating and high-concentration drugs are put in, the incidence of phlebitis is high [3]. On the other hand, with the increasing use of intravenous chemotherapy in cancer patients, long-term intravenous nutrition supporters, and the need

for perennial infusion patients, the peripherally inserted central catheter (PICC) is widely used and irreplaceable in modern medicine [4-6]. According to statistics, the number of catheters in the United States has exceeded 5 million per year, mainly because PICC can effectively alleviate the pain caused by repeated puncture and reduce the risk of peripheral phlebitis, and the catheter is easy to fix and stays for up to 1 year [7]. Despite the many advantages of PICC, there are complications such as infection, thrombosis, phlebitis, catheter displacement, and catheter leakage [8-10]. Among them, venous thrombosis is one of the most common and serious complications, and its incidence

almost reaches 2%-26% [11]. Once a blood clot occurs, the consequences are extremely serious and even life-threatening. Gaddh and other studies have shown that 33%-66% of thrombosis has no clinical symptoms; therefore, patients with occult thrombosis are easily overlooked [12, 13]. Early prevention and early detection are extremely urgent.

At present, it is believed that thrombosis in PICC is mainly caused by mechanical stimulation of the vessel wall, damage to the vascular endothelial cells, initiation of the coagulation system, and a hypercoagulable state of the body [14]. It is clinically used for anticoagulant and antithrombotic drugs, most commonly heparin, aspirin, low molecular weight heparin, and other drugs [15, 16]. Because low molecular weight heparin has the characteristics of small PLT function, lipid metabolism, high safety, long half-life, and no bleeding after use, it has become the most commonly used drug in secondary pathological hypercoagulability [17, 18]. However, there are few reports on prophylactic use of low molecular weight heparin in the PICC. In this study, we hypothesized that preventive application of low molecular weight heparin could ameliorate venous thrombosis in a PICC animal model.

Materials and methods

Experimental animals

40 healthy New Zealand rabbits (weight 12 to 2.5 kg) including 20 females and 20 males were purchased from Hangzhou Scientific Research Cloud Biotechnology Co., Ltd. (Zhejiang, China). All animals were first fed in a single cage at the Animal Experimental Center for 1 week. Our study was approved by the Ethics Committee of Jinhua Polytechnic. This study was carried out in strict accordance with the recommendations in the Guide for the Care and Use of Laboratory Animals of the National Institutes of Health. The animal use protocol was reviewed and approved by the Institutional Animal Care and Use Committee (IACUC) of the Medical University.

Experimental groups

The forty rabbits were randomly divided into 4 groups (n=10, each group): 1) control group: rabbits were injected subcutaneously with normal saline once a day for 7 days; 2) low concentration low molecular weight heparin group:

rabbits were injected subcutaneously with 50 U/kg low molecular weight heparin sodium once daily for 7 days; 3) medium concentration low molecular weight heparin group: rabbits were injected subcutaneously with 100 U/kg low molecular weight heparin sodium once daily for 7 days; 4) high concentration low molecular weight heparin group: rabbits were injected subcutaneously with 200 U/kg low molecular weight heparin sodium once daily for 7 days. After that, all rabbits were used for the construction of a PICC animal model.

PICC animal model

First, rabbits were weighed, followed by anesthesia. Skin was prepared around the ear vein and anesthetized with a 3 ml sodium pentobarbital solution 1 ml/kg (final concentration 30 mg/kg). Next, the tube in the ear vein was placed. In brief, the rabbit PICC catheter insertion length was measured after the rabbit was completely anesthetized. The measurement method was as follows: the rabbit was in a supine position, and the ears were upright and 180° parallel to the body, starting from the puncture point to the most obvious stop of the beat of the heart, about 21-26 cm. After the skin preparation, disinfection, puncture, the tube was sent to the predetermined length, the patency was checked and it was preliminarily fixed. Next, after injecting about 0.5 ml of imported lipiodol with a sheath and confirming the anterior vena cava by X-ray, a blood sample of 1.8 ml was collected. Finally, the catheter was punched with 10 ml of physiological saline, and the catheter was closed and fixed with 3 M. To prevent accidental extubation of the rabbit ear catheter, the small animal Elizabeth ring was externally placed so as not to affect blood circulation and rabbit feeding. After the model was successfully divided into 4 groups, 10 rabbits in each group were taken 1 week after indwelling, blood samples were taken, PICC tubes were removed, and three sections were excised in the anterior, middle, and posterior portions of the catheter by surgical methods, with an average length of about 5 cm. Two segments of the ear vein and the anterior vena cava were taken, each of which was about 3 cm long, and a total of 5 living specimens were fixed in 10% formaldehyde. Ten rabbits in each group were euthanized at each time point. Sodium pentobarbital was injected intravenously (100 mg/kg).

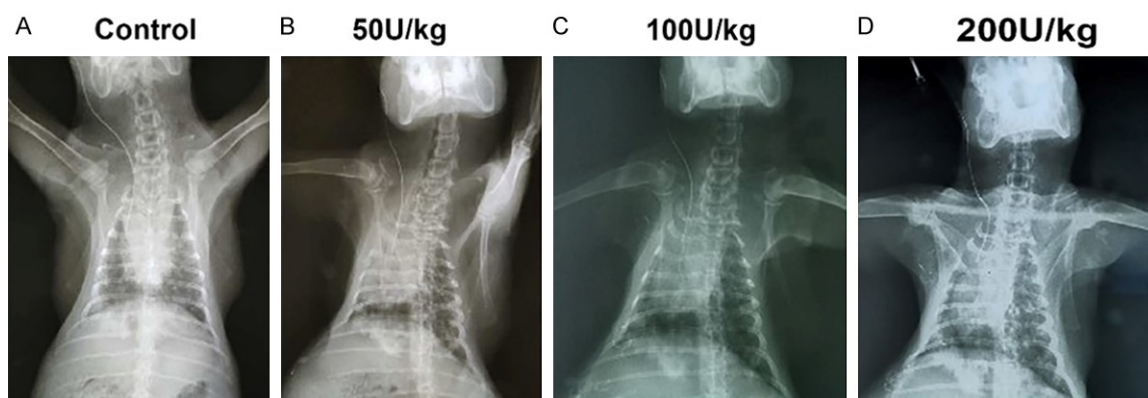


Figure 1. X-ray results showing the successful construction of PICC model.

PICC model evaluation

The criteria for successful establishment of the PICC animal model were as follows: one puncture was successful; local injury-free, oozing; the end of the catheter was not distorted, folded, and left in the anterior vena cava of the rabbit. The mental condition, appetite, activity and local presence or absence of wounds, redness, swelling, exudation and other conditions were observed.

Hematoxylin and eosin (H&E)

Ear vein, anterior vena cava, and catheter of rabbits were fixed in 10% formalin solution for 24-48 h. After that, the ear vein, anterior vena cava, and catheter were dehydrated by 70%, 80%, 90%, 95%, 100% ethanol I, 100% ethanol II for 52 min, respectively. Then, the ear vein, anterior vena cava, and catheter were immersed transparently using xylene I and xylene II for 52 min, respectively. After being immersed in wax, the ear vein, anterior vena cava, and catheter were embedded and sliced. The section thickness was 4 μ m. After the sections were placed in a 60°C box for 6-12 h, the tissues were subjected to H&E staining. After dewaxing to water, the section was stained with hematoxylin dye solution for 20 min at room temperature and eosin solution for 1 min. After dehydration and transparency, the sections were taken out and sealed with a neutral balsam.

Enzyme-linked immunosorbent assay (ELISA)

According to manufacturer's instructions, D-dimer (D2D) and fibrinogen (FG) were collected

from the supernatant of rabbit blood and were measured using the ELISA test kit (MultiSciences Biotech Co., Ltd., China).

Biochemical testing

The ear vein blood sample was taken, and the prothrombin time (PT), activated partial thromboplastin time (APTT), and thrombin time (TT) were detected by a fully automatic coagulation analyzer.

Statistical analysis

All statistical analyses were performed using Graphpad Prism 7.0. Data are expressed as the mean $\pm$ SD. The differences between two groups were analyzed using Student's t test. *P*-value <0.05 was considered significant.

Results

The construction of PICC model

After the PICC model was constructed, we observed that the mental status, appetite, and activity of the rabbits in each group were good. Furthermore, the wounds did not show obvious redness and exudation. X-ray results showed that the PICC model of each group of rabbits was successfully constructed (**Figure 1A-D**).

Preventive application of low molecular weight heparin ameliorates the pathologic damage to ear vein in PICC model

In the control group, we observed irregular rupture of the intima of the ear vein, intimal fibrosis, scar formation, and near-occlusion of the lumen, with a small amount of bleeding (**Figure**

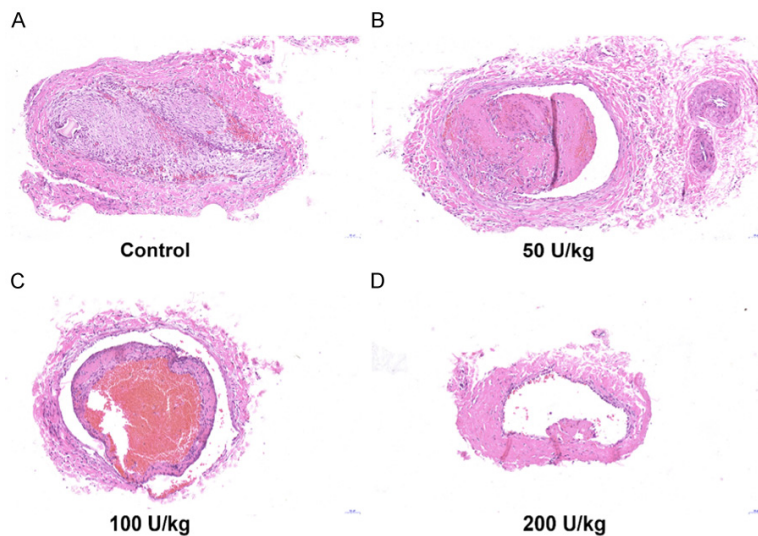


Figure 2. H&E showing that preventive application of low molecular weight heparin ameliorates the pathological damage of ear vein in PICC model. A. Control group; B. 50 U/kg low-concentration low molecular heparin sodium group; C. 100 U/kg medium-concentration low molecular heparin sodium; D. 200 U/kg medium-concentration low molecular heparin sodium.

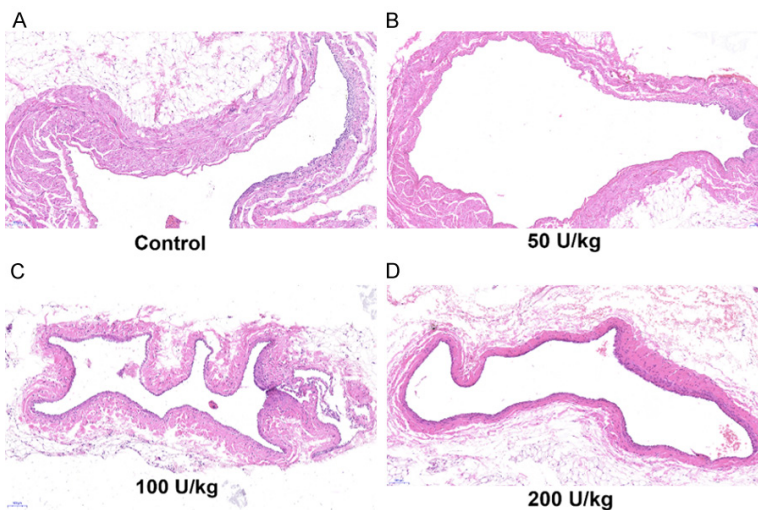


Figure 3. H&E showing that preventive application of low molecular weight heparin ameliorates the pathological damage of anterior vena cava in PICC model. A. Control group; B. 50 U/kg low-concentration low molecular heparin sodium group; C. 100 U/kg medium-concentration low molecular heparin sodium; D. 200 U/kg medium-concentration low molecular heparin sodium.

2A). In the low-concentration low molecular weight heparin (50 U/kg) group, we found that there was a scar in the lumen of the ear vein, the middle membrane and the outer membrane had no obvious lesions, and the lumen was not completely occluded (**Figure 2B**). In the medium-concentration low molecular weight heparin (100 U/kg) group, we observed a slight rupture of the wall of the ear vein, a scar and

thrombus in the lumen, and the lumen was not completely occluded (**Figure 2C**). In the high-concentration low molecular weight heparin (200 U/kg) group, the results showed that the ear veins were relatively intact, there was no obvious scar in the lumen, no obvious thrombosis, and the lumen was unobstructed (**Figure 2D**).

Preventive application of low molecular weight heparin ameliorates the pathologic damage of anterior vena cava in PICC model

In the model control group, the results showed that the intima of the anterior vena cava was irregularly ruptured, and the wall was thickened with severe inflammatory cell infiltration (**Figure 3A**). In the 50 U/kg low-concentration low molecular weight heparin group, we found that the intima of the anterior vena cava was relatively intact, and the wall was slightly thickened with a small amount of inflammatory cell infiltrate (**Figure 3B**). In the 100 U/kg medium-concentration low molecular weight heparin group, we observed that the intima of the anterior vena cava was intact and the wall was normal with a small amount of inflammatory cell infiltrate (**Figure 3C**). In the 200 U/kg high-concentration low molecular weight heparin group, the intima of the anterior vena cava was intact and the wall

was normal with a small amount of inflammatory cell infiltrate (**Figure 3D**).

Preventive application of low molecular weight heparin inhibits venous thrombosis in a PICC model

In the model control group, we found that there was a thrombus in the catheter and it filled the

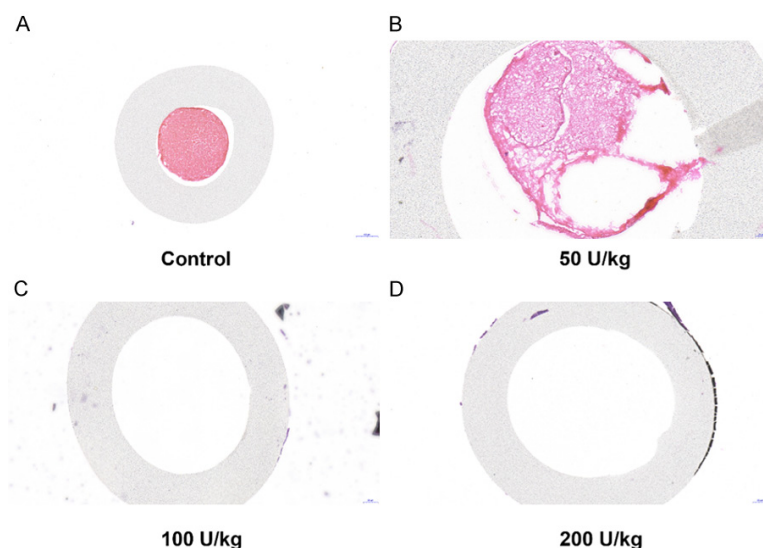


Figure 4. H&E showing that preventive application of low molecular weight heparin inhibits venous thrombosis in PICC model. A. Control group; B. 50 U/kg low-concentration low molecular weight heparin sodium group; C. 100 U/kg medium-concentration low molecular weight heparin sodium; D. 200 U/kg high concentration low molecular weight heparin sodium.

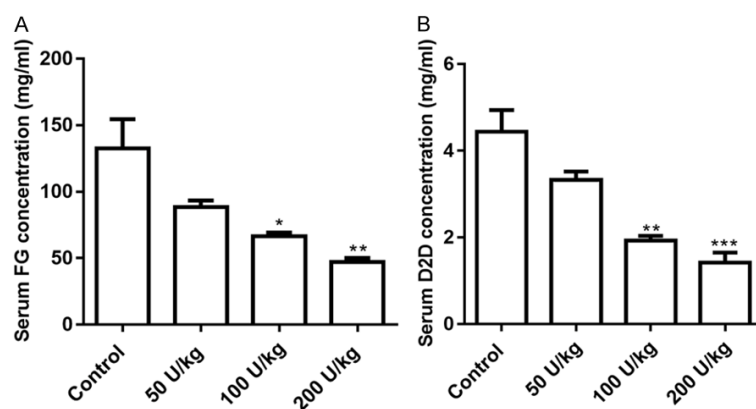


Figure 5. Preventive application of low molecular weight heparin significantly inhibits serum FG and D2D levels in PICC model. A. FG; B. D2D. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

lumen (**Figure 4A**). In the 50 U/kg low-concentration low molecular weight heparin group, a thrombus was formed in the inner portion of the catheter (**Figure 4B**). In the 100 U/kg medium and 200 U/kg high concentrations of low molecular weight heparin, there was no thrombus in the catheter (**Figure 4C, 4D**).

Preventive application of low molecular weight heparin significantly inhibits serum FG and D2D levels in PICC model

Serum FG and D2D levels in PICC model were examined using ELISA assay. The results

showed that low molecular weight heparin significantly inhibited the levels of FG in the serum of PICC model compared to control group, with a concentration-dependent manner (**Figure 5A**). Furthermore, we also found that the levels of D2D in the serum of PICC model were significantly inhibited compared to control group, in a concentration-dependent manner (**Figure 5B**).

Preventive application of low molecular weight heparin significantly elevates PT, APTT, and TT in PICC model

Biochemical testing results showed that low molecular weight heparin significantly elevated PT, APTT, and TT in the ear vein blood of PICC model, in a concentration-dependent manner (**Figure 6A-C**).

Discussion

Based on the current clinical research on venous thrombosis in PICC, the basic research is minimal, the symptomatic treatment is the mainstay, and preventive intervention is lacking. This study aimed to further explore the possible mechanism of PICC venous thrombosis and preventive application of low molecular

weight heparin. We constructed a PICC model. The antithrombotic effect of low molecular weight heparin was evaluated by observing the pathologic changes of the venous lumen and the coagulation measurements including FG, D2D, PT, APTT, and TT. Our findings revealed that preventive application of low molecular weight heparin significantly ameliorated PICC venous thrombosis.

PICC is usually placed in the arm, under the clavicle, or in the jugular vein and terminates in the superior vena cava. It is frequently used for prolonged drug administration. A common indi-

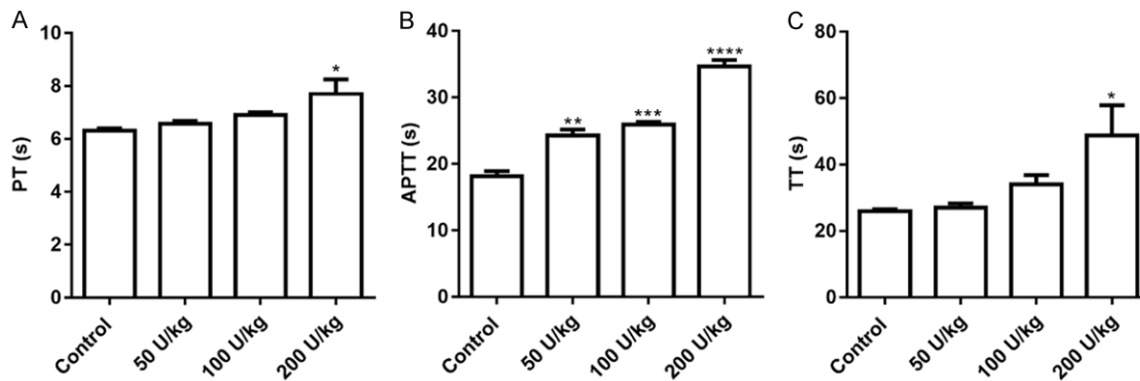


Figure 6. Preventive application of low molecular weight heparin significantly elevates PT, APTT, and TT in PICC model. A. PT; B. APTT; C. TT. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$; **** $P < 0.0001$.

cation for PICC is ongoing chemotherapy in cancer patients. However, the main complication of its placement is thrombosis. Therefore, in this study, rabbits were injected prophylactically with low molecular weight heparin once daily for 7 days. After that, the PICC model was successfully constructed according to X-ray.

We observed the pathological changes of the ear vein and anterior vena cava. Our results showed that after preventive application of low molecular weight heparin, the pathologic changes were significantly improved in the PICC model. Furthermore, we found that low molecular weight heparin significantly inhibited venous thrombosis in the PICC model. These results indicate that preventive application of low molecular weight heparin can prevent venous thrombosis in PICC. Since low molecular weight heparin can specifically act on blood coagulation factor Xa in vivo, it has a strong antithrombotic effect [19]. Furthermore, low molecular weight heparin stimulates vascular endothelium to release plasminogen activator, enhances fibrinolysis, and weakens the aggregation of platelets [20-22]. Thus, it can reduce blood hypercoagulability and enhance anticoagulant effect. Some studies have shown that low molecular weight heparin combined with other drugs, such as dexamethasone, tranexamic acid, etc., but the combined effect was not statistically different compared with a single use [23, 24]. Also mentioned were the dosage and treatment of low molecular weight heparin, which was administered subcutaneously or intravenously at 100 U/kg once a day for 7-10 days [25-27]. In this study, we examined serum FG and D2D levels using ELISA.

Consistent with previous studies, we found that low molecular weight heparin significantly inhibited serum FG and D2D levels in a PICC model, in a concentration-dependent manner. Long-term low molecular weight heparin anticoagulant therapy has been shown to modulate thrombin generation and D2D in patients with cancer and venous thromboembolism [17, 28]. Furthermore, it has been reported that low molecular weight heparin significantly serum FG levels in obstructive pulmonary disease rat models [29]. To observe the anticoagulant effect of low molecular weight heparin, biochemical testing was carried out, including PT, and TT. The results showed that low molecular weight heparin significantly elevated PT, APTT, and TT in the ear vein blood of PICC model, in a concentration-dependent manner. Consistently, previous studies have found that low molecular weight heparin improved PT, APTT, and TT in different venous thrombosis models [30-32].

In this study, we investigated the effects of preventive application of low molecular weight heparin on venous thrombosis in a PICC model. Our results indicated that preventive application of low molecular weight heparin could ameliorate PICC-related venous thrombosis, which requires further exploration.

Conclusion

In summary, our study found that preventive application of low molecular weight heparin significantly could ameliorate venous thrombosis in PICC model. Our findings could provide insight and evidence for timely prevention and treatment of PICC venous thrombosis.

Acknowledgements

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Disclosure of conflict of interest

None.

Abbreviations

PICC, Peripherally inserted central catheter; H&E, Hematoxylin and eosin; PT, prothrombin time; APTT, activated partial thromboplastin time; TT, thrombin time; D2D, D-dimer; FG, fibrinogen; ELISA, Enzyme-linked immunosorbent assay.

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