Is arginine supplementation effective in preventing preeclampsia in pregnant women?

A suplementação de arginina é efetiva em prevenir pré-eclâmpsia em gestantes?

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ABSTRACT

Objectives: The objective of this study was to review data from randomized controlled trials to assess whether or not the supplementation of L-Arginine (L-Arg) is effective in reducing the incidence of preeclampsia (PE) in pregnancies at risk of developing the disorder. **Methods:** We aimed to systematic review randomized controlled trials, including those which compared L-Arg supplementation with placebo in pregnant women at high risk of PE development, analyzing PE incidence as the main outcome. Data were collected from MEDLINE/ Pubmed, EMBASE/ Elsevier, LILACS/ BVS and Cochrane. **Results:** A total of 46 papers were identified in the primary search. After analysis of eligibility, inclusion and exclusion criteria, two articles (which respected in detail all the stages of evaluation) were included in the present review. A risk of bias assessment was performed. Data analysis revealed that the incidence of PE was significantly lower in both studies, and no major adverse effects were reported. The limitations of this study were the lack of standardization between the trials analyzed and the relative low number of studies included. **Conclusions:** The supplementation with L-Arg appears to reduce the incidence of PE in pregnant women with high risk for its development.

Keywords: Pregnancy, Arginine, Preeclampsia, Supplementation, Nitric oxide.

RESUMO

Objetivo: O objetivo deste estudo foi revisar dados de ensaios clínicos randomizados para avaliar se a suplementação de L-Arginina é efetiva para reduzir a incidência de pré-eclâmpsia em gestantes com alto risco de desenvolver a doença. **Métodos:** Realizamos uma revisão sistemática de ensaios clínicos randomizados, incluindo aqueles que compararam a suplementação de L-Arginina com placebo em gestantes de alto risco de desenvolvimento de pré-eclâmpsia, analisando a incidência de pré-eclâmpsia como desfecho principal. Os estudos foram selecionados do MEDLINE/ Pubmed, EMBASE/ Elsevier, LILACS/ BVS e Cochrane. **Resultados:** Um total de 46 estudos foram identificados na busca primária. Após análise da elegibilidade, dos critérios de inclusão e de exclusão, dois artigos (que respeitaram em detalhes todas etapas de avaliação) foram incluídos na presente revisão. Foi realizada uma avaliação de risco de viés. A análise dos dados revelou que a incidência de pré-eclâmpsia foi significativamente menor em ambos os estudos, e nenhum efeito adverso importante foi relatado. As limitações deste estudo foram a falta de padronização entre os ensaios clínicos analisados e o número relativamente baixo de estudos incluídos. **Conclusão:** A suplementação com L-Arginina parece reduzir a incidência de pré-eclâmpsia em gestantes de alto risco para seu desenvolvimento.

Palavras-chave: Gravidez, Arginina, Pré-eclâmpsia, Suplementação, Óxido nítrico.

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INTRODUCTION

L-arginine (L-Arg) is a conditionally essential amino acid[1] obtained through diet, as well as protein turnover and endogenous synthesis. The main dietary sources are foods such as seafood, seeds, nuts, meats, concentrated rice protein and isolated soy protein. Initially, about 40% of the ingested L-Arg is degraded by first-pass metabolism in the liver[2], therefore not all oral L-Arg ingested enters the plasma circulation in its free form.

The endogenous synthesis of Arg corresponds to 10 to 15% of the total body L-Arg and occurs from the amino acids glutamine, glutamate and proline, which are converted to citrulline inside the mitochondria of enterocytes[2]. Citrulline is then converted into L-Arg, mainly in the kidneys. However, endogenous synthesis is not sufficient to supply all L-Arg needs on certain occasions, such as infection, inflammation or conditions that affect renal or intestinal metabolic function. In addition, in diseases that affect any of the enzymes in the urea cycle, L-Arg becomes an essential amino acid[3].

Most part of free L-Arg comes from protein turnover, corresponding to approximately 85% of circulating L-Arg[4]. The term "protein turnover" refers to both protein synthesis and degradation, as well as its exchanges between compartments of the body. After protein formation, changes in specific amino acids may occur due to post-translational modifications (PTMs), resulting in new biological substances[5]. The L-Arg that constitutes histones can undergo such epigenetic changes, mainly through citrullination and methylation. The enzymatic methylation of L-Arg generates symmetrical and asymmetric forms of L-Arg: Symmetric Dimethylarginine (SDMA), NG-monomethyl-L-arginine (L-NMMA) and Asymmetric Dimethylarginine (ADMA)[6,7].

Methylated arginines interfere with the transport of L-Arg, directly impairing the synthesis and bioavailability of nitric oxide (NO)[8], since L-NMMA and ADMA have a competitive inhibitory action and promote the decoupling of the three isoforms of the nitric oxide synthase (NOS) enzyme[7]. NOS endothelial isoform (eNOS) converts L-Arg into NO and L-citrulline in the presence of oxygen and the cofactor tetrahydrobiopterin. NO can also be produced by alternate enzymatic and non enzymatic pathways[9,10]

NO was described as an endothelium derived relaxing factor (EDRF)[11,12] it has been shown to have autocrine and paracrine effects, being the main vasodilator of the placenta and acts as a regulator of fetoplacental blood flow. It is important for occurence of vasculogenesis, mediating the expression of vascular endothelial growth factor (VEGF), in addition to contributing to angiogenesis, since it stimulates other angiogenic factors[13]. NO, obtained from eNOS, when directed to smooth muscle cells, activates the enzyme guanylate cyclase that converts guanosine triphosphate (GTP) into cyclic guanosine monophosphate (cGMP)[12,14]. After that, there is a decrease in free calcium concentration in the muscle cells and subsequent relaxation of the smooth muscles, resulting in vasodilation[12]. The elevation of cGMP also leads to antiplatelet effects[12,14], and is related to the induction of apoptosis in smooth muscle tissue[7,15], in addition to suppression of proinflammatory genes[7,16].

Preeclampsia (PE), a condition which affects about 2 to 5% of pregnant women, is one of the main causes of maternal mortality, especially in developing countries[17]. Its genesis is currently theorized as a process of improper cytotrophoblastic placental invasion, resulting in imbalance between angiogenic and antiangiogenic factors. When this happens, there is a reduction in the supply of nutrients and oxygen to the fetus and ischemia[18], in addition to the creation of a system of high vascular resistance. It has been observed that women with PE have higher ADMA concentrations, which could impact on NO availability, leading to oxidative stress and endothelial dysfunction[8,19]. L-Arg supplementation provides an increase in the L-Arg/ADMA ratio, in order to increase the availability of NO[15]. Therefore, it has been hypothesized that the administration of L-Arg could reduce the incidence of PE in women at high risk for its development[20]. The objective of this systematic review is to analyze the placebo-controlled randomized clinical trials found in the literature that study the effectiveness of prophylactic L-Arg supplementation in reducing the incidence of PE in women at high risk for its development.

MATERIALS AND METHODS

A systematic review of randomized clinical trials was conducted to assess the use of prophylactic L-Arg to reduce the incidence of PE.

For the review process, we used the Preferred Reporting Items for Systematic Reviews and Meta-Analyzes (PRISMA) perspective, as well as its checklist, respecting all the steps it suggested[21]. The objectives were based on the PICO strategy (Population; Intervention; Comparisons; Outcomes), as well as the choice of descriptors[22]. The bibliographic research was performed using the following databases: MEDLINE / Pubmed, EMBASE / Elsevier, LILACS / Biblioteca Virtual en Salud (BVS) and Cochrane Controlled Trials Register (CENTRAL). Resulting in articles available from 2006 until october 24, 2020 (final date of data retrieval).

The choice of Health Sciences Descriptors (DeCS) derived from the PICO strategy, using the terms "pregnancy" (population), "arginine" (intervention), "placebos" (control) and "preeclampsia" (outcome). The Medical Subject Headings (MeSH) were also used to refine search on the MEDLINE database (PubMed). For the search on EMBASE, synonyms for search sensitization were also applied. Table 1 shows the sensitized search entries[23] that were used for search in MEDLINE / PubMed. In LILACS, DeCS terms were used in both English and Portuguese.

Studies published up to the date of the search were identified, without language restrictions. For this review, a data extraction spreadsheet was developed, corresponding to a study eligibility sheet, describing its type, inclusion criteria, exclusion criteria, number of participants, clinical outcomes analyzed, quality of studies, and possible biases. An initial evaluation was carried out separately by two examiners, with a final decision by a third reviewer in case of disagreement between the first two reviewers. The risk of bias in the studies was individually analyzed using the Cochrane Risk of Bias Tool[24] to determine whether biases were present in the study level. This tool was used to determine if the study was considered adequate to be included in this review.

As initial identification criteria, we analyzed placebo-controlled randomized clinical trials which used supplementation containing L-Arg by any route of administration and had the prevention of PE as a primary outcome.

The exclusion criteria were: studies in animals, studies that involved supplementation of L-Arg precursors, abstracts from annals of congresses or symposia and book chapters. We followed in detail all the documentation steps of the identified, selected, included and excluded articles.

Table 1. Search strategy applied on MEDLINE/PubMed

MEDLINE/PubMed **Sensitized MeSH terms** **Population: pregnant women under the risk for preeclampsia development**
(Pregnancy[MeSH Terms]) OR (Pregnancies) OR (Gestation) OR (Pregnancy, High-Risk) OR (Pregnancy, High Risk) OR (Pregnancies, High-Risk) OR (Pregnancy)
AND **Intervention: L-Arginine supplementation**
(Arginine[MeSH Terms]) OR (L-Arginine)) OR (arginine)
AND **Control: Placebo**
(Placebo[MeSH Terms]) OR (Placebo)
AND **Outcome: preeclampsia prophylaxis**
((Preeclampsia[MeSH Terms]) OR (Pregnancy Toxemias) OR (Pregnancy Toxemia) OR (Edema-Proteinuria-Hypertension Gestosis) OR (Edema Proteinuria Hypertension Gestosis) OR (Toxemia Of Pregnancy) OR (Toxemia Of Pregnancies) OR (EPH Complex) OR (EPH Toxemia) OR (EPH Gestosis) OR (Eclampsia) OR (Eclampsias) OR (Pregnancy-Induced Hypertension) OR (Induced Hypertension Pregnancy) OR (Induced Hypertensions, Pregnancy) OR (Gestational Hypertension) OR (Preeclampsia)) AND ((prophylaxis[MeSH Terms]) OR (preventive therapy) OR (prevention and control) OR (preventive measures) OR (prevention) OR (control) OR (prophylaxis))
AND **Filter for randomized controlled trials**
randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized controlled trials [mh] OR random allocation [mh] OR double-blind method [mh] OR single-blind method [mh] OR clinical trial [pt] OR clinical trials[mh] OR ("clinical trial"[tw]) OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR (placebos [mh] OR placebo* [tw] OR random* [tw] OR research design [mh:noexp] OR comparative study [pt] OR control* [tw] OR prospective* [tw] OR volunteer* [tw]) NOT (animals [mh] NOT humans [mh])

The definition of PE has changed over the course of the analyzed period of time (2006-2020)[25]. Although we used the ISSHP 2018 definition for interpretation purposes, studies that used other definitions, which had proteinuria as a necessary point for the diagnosis, were not excluded.

We considered the risk ratio and number needed to treat (NNT) as the main summary measures to assess the efficacy of L-Arg supplementation to reduce PE incidence. P values of < 0.05 were considered statistically significant.

Due to the nature of the review study, no approval was required by the Research Ethics Committee.

RESULTS

For the proposed review, the descriptors were used in the four databases, which resulted in a total of 46 selected articles: 9 articles in MEDLINE / Pubmed; 9 articles in EMBASE / Elsevier; 8 in LILACS / Biblioteca Virtual en Salud (BVS); and 20 in the Cochrane Controlled Trials Register (CENTRAL). Respecting the eligibility criteria, 18 were identified as duplicates and 24 were excluded using the exclusion criteria, thus 4 articles were kept for the next steps. After abstract screening these articles as to their relevance and thematic focus, all 4 articles were selected to be read in full. The reading of each article in its entirety was performed by 2 reviewers, and a third reviewer resolved disagreements about the inclusion of the article. Two articles met the inclusion criteria for the present review (Figure 1).

The two clinical trials included, both of Mexican origin, are dated 2011 and 2016, written by Vadillo-Ortega et al.[20] and Camarena Pulido et al.[26], respectively. The risk of bias in the studies was individually analyzed using the Cochrane Risk of Bias Tool [24] (Table 2). Although in one of the clinical trials, by Vadillo-Ortega et al.[20], L-Arg was not used in isolation, but combined with vitamins in a meal bar, which might confuse the analysis, we considered the quality of the analyzed studies to be adequate.

Vadillo-Ortega et al. (2011) were the first to evaluate the efficacy of prophylactic L-Arg supplementation to reduce the incidence of PE through a randomized controlled clinical trial.

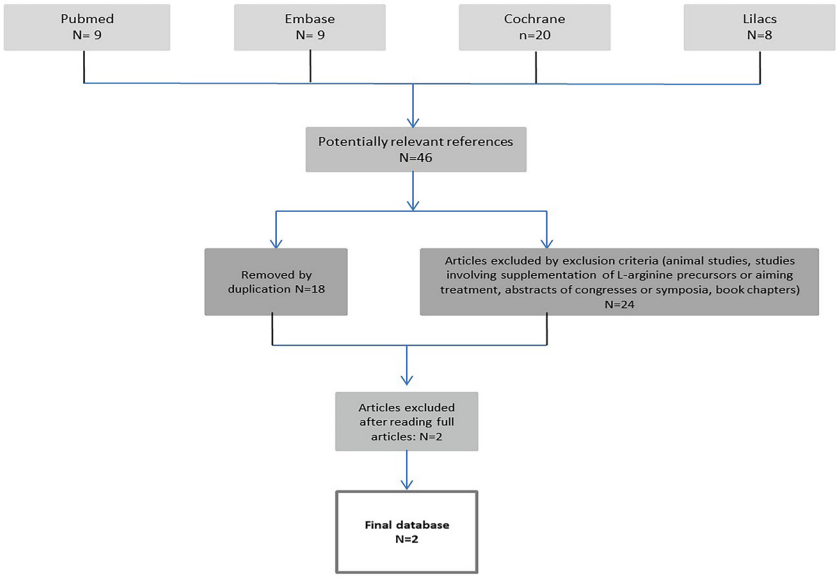

Figure 1. Search Results

Table 2. Bias Risk Analysis

Bias Risk							
Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Vadillo-Ortega et al.	Low	Low	Low	High	High	Low	Unclear
Camarena et al.	Low	Low	Low	Low	Low	Low	Unclear

They analyzed 672 women with an increased risk of PE (e.g., previous history of PE or family history of the disease in first-degree relatives) between the fourteenth and thirty-second weeks of gestation. Women whose fetuses had known abnormalities, as well as those who had multiple pregnancy, diabetes mellitus or gestational diabetes mellitus, pre-existing systemic arterial hypertension, pre-existing kidney disease, collagen diseases, current, previous or family history of cancer or other diseases that needed treatment were excluded[20].

Patients were allocated into one of three groups: to receive supplementation via a food bar containing L-Arg and antioxidant vitamins; antioxidant vitamins only; or placebo only. Each supplement bar in the L-Arg group contained 3.3g of the amino acid, and the patients were instructed to eat two bars per day (6.6g of L-Arg / day), from the date of study allocation (14th to 32nd week of gestational age) until the date of delivery[20].

The main outcome analyzed was the incidence of PE, defined by Vadillo-Ortega et al. (2011) as the development of hypertension (systolic pressure ≥140 mmHg, diastolic pressure ≥90 mmHg or both) accompanied by proteinuria (> 300mg / 24h) after the 20th week of gestation in previously normotensive women. The incidence was significantly lower (χ^2 = 19.41, p <0.001) when comparing L-Arg + vitamins with placebo, with a relative risk of 0.42 (95% CI: 0.28-0.62, p <0.0001). The number needed to treat (NNT) was 5.73 (95% CI 4.0-10). When comparing the group receiving vitamin-associated L-Arg with the group receiving only vitamins, the L-Arg group had a relative risk of 0.56 (95% CI: 0.37-0.85, p = 0.004), with a NNT of 10.20, (95% CI: 6-36)[20].

Camarena Pulido et al. (2016), in a double-blind randomized controlled clinical trial with 100 pregnant women identified as high risk for developing PE (nulliparous, prior history of PE, chronic hypertension, and BMI greater than or equal to 30), performed pre- and post-intervention assessments to analyze maternal and fetal health by Doppler ultrasound and blood sampling. Exclusion criteria were patients who did not follow the study guidelines; who did not attend two consecutive medical appointments; and those who ingested alcohol, drugs, or who were taking medications concomitant with the study. The intervention consisted in the use of 3g of L-Arg orally daily from the 20th week of pregnancy[26].

The main outcome analyzed was the occurrence of PE, defined as the development of hypertension (systolic pressure ≥140 mmHg, diastolic pressure ≥90 mmHg or both) accompanied by proteinuria (> 300mg / 24h) after the 20th week of pregnancy in previously normotensive women[26].

They were evaluated from the twentieth week of gestation, every three weeks until delivery, after delivery, and were followed for an additional two weeks, with clinical evaluation, laboratory and ultrasound tests performed in all appointments to assess the development of hypertensive disorders of pregnancy. The relative risk for the group receiving L-Arg was 0.26 (95% CI 0.07-0.87) when compared to placebo, with a number needed to treat (NNT) of 6 (95% CI 3-29)[26].

DISCUSSION

The present review aims to study the efficacy of L-Arg supplementation in reducing the incidence of PE. According to the International Society for the Study of Hypertension in Pregnancy (ISSHP), PE can be defined as the development of hypertension (systolic pressure ≥ 140 mmHg or diastolic pressure ≥ 90 mmHg) after 20 weeks of gestational age associated with one or more of the conditions of proteinuria, maternal organ dysfunction or placental uterine dysfunction including: Acute kidney injury (creatinine ≥90umol/L; 1 mg/dL); Liver involvement (elevated transaminases, eg, alanine aminotransferase or aspartate aminotransferase >40 IU/L) with or without right upper quadrant or epigastric abdominal pain; Neurological complications (examples include eclampsia, altered mental status, blindness, stroke, clonus, severe headaches, and persistent visual scotomata); Hematological complications (thrombocytopenia–platelet count < 150 000/μL, disseminated intravascular coagulation, hemolysis); Uteroplacental dysfunction (such as fetal growth restriction, abnormal umbilical artery Doppler waveform analysis, or stillbirth)[25]. This definition, however, was not the definition used by the two trials analyzed by this review, since proteinuria was a fundamental condition to define PE before 2016[20,25,26].

Due to the absence of autonomic control in the fetal-placental vascular system that occurs during pregnancy, the bioavailability of NO is the main vasodilator agent of the placenta. NO activates the enzyme guanylate cyclase, which converts GTP into cGMP, leading to a decrease in calcium concentration in the muscle cells, resulting in vasodilation[12].

This process plays a fundamental role for both the pregnant woman and the fetus, being essential in cytotrophoblastic invasion, embryo development, fetal growth and placental vascularization.[18,27]

NO also prevents platelet adhesion and aggregation and interferes with smooth muscle cell proliferation by inducing their apoptosis[7,12,15,28]. It has been hypothesized that in a state of oxidative stress, the overproduction of reactive oxygen species (ROS) exceeds the individual's antioxidant defense mechanisms, causing rapid inactivation of eNOS and generating a reduction in the bioavailability of vascular NO[16].

In women with PE, lower NO availability is observed in some studies, being associated with maternal outcomes such as greater peripheral vascular resistance, higher blood pressure levels, as well as placental alterations, such as vasoconstriction and reduced placental perfusion[18,29,30]. However, some studies found conflicting results, probably due to difficulties in measuring NO due to its short half-life[19].

Due to chronic placental hypoperfusion present in PE, there is excessive release of antiangiogenic proteins, such as soluble placental tyrosine kinase-1 (sFlt-1), and reduction of proangiogenic substances, such as vascular endothelial growth factor (VEGF) occurs[18,31,32]. Thus, patients with this condition undergo increased oxidative stress and a hyperinflammatory state, favoring the development of endothelial dysfunctions, vasospasm and impairment in placental angiogenesis[18].

In addition, higher concentrations of ADMA, a metabolic derivative of L-Arg that has pro-inflammatory and harmful effects on the vascular endothelium, impairing NO synthesis, are found in women with PE when compared to healthy pregnancies[29,33]. The increase in ADMA levels occurs even before the development of PE, which suggests that women with high risk for PE development may have higher ADMA concentrations[13].

Thus, it was hypothesized that the use of L-Arg, an important precursor in the NO cycle, could be useful in increasing NO bioavailability by competing with ADMA for binding to the eNOS enzyme[15]. Camarena Pulido et al. found that low doses of L-arg were sufficient to increase NO bioavailability[26].

This review analyzed two randomized clinical trials found in the literature that addressed the supplementation of the amino acid L-Arg for PE prophylaxis. Both studies found statistically significant results for the association of L-Arg use and the primary outcome of PE prevention. In addition, it is worth mentioning that the two studies used different doses at different gestational ages in their interventions. In the study by Vadillo-Ortega et al., however, there was no intervention with isolated L-Arg, but a protein bar composed of L-Arg associated with antioxidant vitamins allowing one to question whether the results derived from just one of them or from the association of both. However, the reduction in the incidence of PE was observed only in the group that received the supplement bar with L-Arg and vitamins, with no reduction in the group that received only vitamins[20].

In the study by Vadillo-Ortega et al.[20], a significantly higher incidence of adverse effects was observed in the group of patients who ingested L-Arg bars with antioxidant vitamins, when compared to the placebo group. The most reported side effects were nausea ($p = 0.019$), dyspeptic symptoms ($p = 0.04$), palpitations ($p = 0.019$), dizziness ($p = 0.039$) and headache ($p = 0.01$). In the study by Camarena Pulido et al.[26], the occurrence of dyspepsia was also significantly higher in the group that received L-Arg than in the placebo group ($p = 0.008$). Other symptoms such as vomiting, diarrhea, abdominal pain have also been reported, but without statistical significance[26]. In both studies, the presence of these symptoms did not result in patients discontinuing or abandoning therapy[20,26].

As for secondary outcomes, both articles showed significant results in reducing prematurity; however they diverged regarding the benefits in APGAR scoring and birth weight. In addition, other outcomes analyzed by Camarena Pulido et al.[26] that showed no statistically significant differences between groups were HELLP syndrome, intrauterine growth restriction (IUGR) and premature rupture of membranes.

Other reviews on this subject found by the authors up to the date of submission of this manuscript did not use the prevention of the development of PE as the main outcome analyzed exclusively. Moreover, this review is the first to analyze the study by Camarena Pulido et al.[26], dated 2016, which was not analyzed by previous reviews.

The limitations of our study are the low number of clinical trials included (2), and the possible bias in one of the studies that did not perform an intervention with only L-Arg supplementation. Also, no additional statistical analysis was performed. Furthermore, the ISSHP definition of PE used by both Camarena Pulido et al. (2016) and Valdillo-Ortega et al. (2011) was recently changed, this could potentially change study design and outcomes in upcoming studies[20,25,26].

The authors of the present study believe that the theoretical basis of the biochemical mechanisms involved in the prophylaxis of PE through L-Arg supplementation means that there is a reasonable pre-test probability that L-Arg supplementation is effective in reducing incidence of PE. The clinical trials analyzed in this review corroborate the hypothesis that there is a positive relation between PE reduction and L-Arg supplementation. However, more studies are needed to analyze this association, so that, if there is any proven benefit, well-defined subgroups are established, separated by gestational age, in order to assess the supposed greater window of opportunity in relation to aspirin, verified by Camarena Pulido et al.[26]. Standardization of L-Arg dosage in clinical trials is also necessary, so that strategies for employing the substance in clinical practice can be created.

The use of L-Arg supplementation in association with acetyl salicylic acid also deserves to be investigated, since there is robust evidence to support the use of acetyl salicylic acid for this purpose[34], and there is a theoretical possibility that the combined use of the two substances has positive impact on PE prophylaxis.

CONCLUSION

The evidence found in the literature leads to the conclusion that L-Arg reduces the incidence of PE in pregnant women with high-risk conditions.

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