Review

Higher incidences of neuropathic pain and altered sensation following radial forearm free flap: A systematic review

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Summary  Background: The radial forearm free flap (RFFF) has been used extensively for complex tissue defect reconstructions; however, the potential for significant donor-site morbidity remains a major drawback. Despite an abundance of literature on donor-site morbidities, no consensus has been reached on exact incidences of sensory morbidities that vary largely between 0% and 46%. Incidences of neuropathic pain in the donor site following RFFF still lack, even though clinical experience shows it often occurs. Therefore, the purpose of this systematic review was to identify the incidence of neuropathic pain and altered sensation in the hand following harvesting of a RFFF.

Methods: A systematic search was performed in multiple databases (Embase, Medline, Cochrane, Web of Science, and Google Scholar). Studies from 1990 onwards that reported donor-site morbidities following harvest of the RFFF were included. Analyzed parameters included hand pain, hypoesthesia, cold intolerance, hyperesthesia, neuroma formation, paresthesia, sharp sensation loss, light sensation loss, and defect closure.

Results: Of the 987 selected studies, 51 eligible articles were selected. The mean level of evidence was 3 (SD 0.6). Twenty articles reported pain as a donor-site morbidity, and the mean incidence of pain reported was 23% (SD 7.8). Hypoesthesia was reported by 37 articles and had a mean incidence of 34% (SD 25). Locations of pain and hypoesthesia included, amongst others, the area of the radial sensory nerve and the skin graft area. The mean incidences of cold intolerance and hyperesthesia were 13% (SD 13) and 16% (SD 15), respectively.

Conclusion: The results of this systematic review suggest that 23% of all patients are dealing with neuropathic pain in the donor-site following harvest of an RFFF. Future studies should

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therefore focus on the prognostic factors and preventive measures of neuropathic pain to further improve clinical outcomes of this widely used flap.

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Introduction

The radial forearm free flap (RFFF) has been used extensively for complex tissue defects and oncological reconstructions. This flap is considered a workhorse in reconstructive surgery due to its versatility, long vascular pedicle, and ease of harvest. Although the RFFF has shown excellent results at the reconstruction site, one of the major drawbacks of this flap is the potential for significant donor-site morbidity.\(^1\) In a study by De Witt et al., 61% of the patients complained when asked about cosmesis and sensibility of the forearm. Furthermore, 30% suffered from numbness or cold intolerance, and 25% of patients experienced forearm disabilities due to donor-site morbidity.\(^2\)

The superficial position of the sensory branch of the radial nerve is vulnerable to injury when raising the radial forearm flap.\(^1\) Damage to the radial sensory nerve (RSN) can cause sensory changes,\(^3\) giving rise to painful neuromas or loss of sensation and cold intolerance.\(^4\) Patients with this type of peripheral nerve injury have an increased risk of functional disability or chronic pain with subsequent social consequences.\(^5\)

Neuropathic pain could be the reason for the complaints in the majority of patients. However, the donor-site itself, which is often closed with a skin graft, can be cumbersome as well. Skin graft loss and wound breakdown resulting in delayed wound healing and tendon exposure occur in up to 46% of the patients.\(^1,3,6\) Delayed wound healing could also lead to unstable scars, pain, and loss of sensibility.\(^7,8\)

Despite an abundance of literature on these donor-site morbidities, incidences of neurologic complications remain unclear. Sensory morbidities vary largely between 0% and 46%\(^9\) and incidences of neuropathic pain in the donor-site have, to our knowledge, not been reported in the literature. As RFFF surgery is often performed as a part of oncological head and neck reconstructions, follow-up focuses on the survival of the disease or severely disabling complications in the recipient site, including speech and mastication impairment,\(^10\) rather than on pain in the donor-site. Therefore, neuropathic pain in the donor-site is likely to be missed or underdiagnosed. A large retrospective study investigating pain in the donor-site reported an average pain score of 2.5 out of 10, with 10 being the worst pain;\(^11\) however, the authors do not further elaborate on the exact location or origin of the pain. To reduce or prevent sensory donor-site morbidities following RFFF surgery, it is of great relevance to clarify its magnitude first. Therefore, the purpose of this systematic review was to identify the incidence of neuropathic pain and altered sensation in the hand following harvesting of an RFFF.

Methods

Literature search

A systematic search of the literature was performed on (recent search/update) using databases including Embase,
Medline, Cochrane, Web of Science, and Google Scholar on February 27, 2020. The complete search terms are available in the supplementary data (see Appendix 1). The systematic search was conducted in consultation with a medical information specialist from our institution and in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement (PRISMA Guidelines) (see Appendix 2).

Study selection

Two authors (C.H. and L.D.) independently selected articles from 1990 onwards, screening titles, and abstracts for inclusion eligibility. Articles had to meet the following inclusion criteria: RFFF surgery reported donor-site morbidity. Articles were excluded if no donor-site morbidity was reported or if a pedicled radial forearm flap was used. Case reports, case series with less than four patients, cadaver, or non-human studies were excluded as well as non-English manuscripts. Disagreements between authors were discussed and resolved by consensus.

Data extraction and quality scoring

Guidelines from the Oxford Centre for Evidence-Based Medicine (CEBM) were used to score the quality of included articles. The quality of the included articles was assessed by using the NIH tool for case series studies, observational cohort and cross-sectional studies, and randomized controlled trials, which is depicted in Appendices 2-4. From the full-text publications, all aspects of donor-site morbidity of the arm were extracted (pain, hypesthesia, hyperesthesia, cold intolerance, loss of sensation, reduced 2-point discrimination, and neuromas) the closure technique of the donor site, and follow-up time. All analyses were performed with STATA 15.0 (StataCorp, Texas, USA).

Results

Study selection

The literature search identified 987 studies (see Figure 1). After screening the abstracts, 897 studies that did not meet the criteria were excluded. Fifty-one studies were found eligible for inclusion, as depicted in Table 1. Donor-site morbidities of 2,083 patients who had received an RFFF were reported. Most included articles were cohort and cross-sectional studies (n=26), followed by case-series (n=22), and randomized controlled trials (n=2). The mean level of evidence (LOE) was 3 (SD 0.6). Thirty articles (59%) had an LOE of 3, followed by an LOE of 4 in 13 articles (25%), and an LOE of 2 in 8 articles (16%) (see Table 1). For the majority of studies, closure of the defect included skin grafts (78%), followed by skin grafts combined with direct closure (9.8%), direct closure (3.9%), skin grafts combined

| Author, year (LOE) | RFFF cases (n) | Follow-up time (months) |
|--------------------|---------------|-------------------------|
| Bardley et al., 1990 | 100 | 22 |
| Bootz et al., 1994 | 51 | >2 |
| Brown et al., 1996 | 21 | 10 |
| Suominen et al., 1996 | 18 | 13 |
| Suominen and Asko, 1996 | 18 | 13 |
| Chambers et al., 1997 | 21 | >3 |
| Richardson et al., 1997 | 103 | >3 |
| Brown et al., 1999 | 11 | 5 |
| Lutz et al., 1999 | 95 | >6 |
| Nehrer-Tairych et al., 1999 | 13 | 13 |
| Sidebottom et al., 2000 | 68 | >12 |
| Avery et al., 2001 | 25 | 6 |
| Nehrer-Tairych et al., 2002 | 35 | >6 |
| Sakai, 2003 | 9 | N/A |
| De Bree et al., 2004 | 37 | N/A |
| Huang et al., 2004 | 20 | 17 |
| Chen et al., 2005 | 28 | 19 |
| Grinsell et al., 2005 | 51 | >12 |
| Ito et al., 2005 | 23 | >12 |
| Zuidam et al., 2005 | 34 | >9 |
| Ho et al., 2006 | 25 | 26 |
| Kerawala et al., 2006 | 50 | 38 |
| Rowe et al., 2006 | 23 | 64 |
| Selvaggi et al., 2006 | 125 | 43 |
| De Witt et al., 2007 | 50 | >6 |
| Karimi et al., 2007 | 41 | 42 |
| Novak et al., 2007 | 19 | >6 |
| Loreti et al., 2008 | 17 | 21 |
| Thiele et al., 2008 | 53 | >3 |
| Chang et al., 2010 | 12 | 9 |
| Morrissey et al., 2010 | 10 | 10 |
| Davis et al., 2011 | 47 | >24 |
| Lee et al., 2011 | 19 | >12 |
| Avery et al., 2012 | 60 | 60 |
| Jaquet et al., 2012 | 44 | >6 |
| Sinclair et al., 2012 | 60 | 44 |
| Hekner et al., 2013 | 28 | >12 |
| Lane et al., 2013 | 45 | 44 |
| Lee et al., 2013 | 23 | 25 |
| Orlik et al., 2014 | 9 | >24 |
| Schwarzer et al., 2016 | 50 | 3 |
| Foissac et al., 2017 | 20 | 10 |
| Aslam-Pervez et al., 2018 | 12 | 16 |
| Pirlich et al., 2018 | 39 | N/A |
| Wang et al., 2018 | 31 | 5 |
| Bertino et al., 2019 | 15 | N/A |
| Kansy et al., 2019 | 73 | >6 |
| Mashravi et al., 2019 | 13 | 7 |
| Potet et al., 2019 | 101 | >12 |
| Jani et al., 2020 | 52 | 24 |
| Krane et al., 2020 | 136 | >6 |

LOE = level of evidence, RFFF = radial forearm free flap
with flap surgery (2.0%), an anterolateral thigh (ALT)-flap (2.0%), or a bilobed flap (2.0%). In one study (2.0%), the type of closure of the donor-site was not specified. Sensate flaps were used in six studies (12%); however, the majority of the studies (73%) did not elaborate on the innervation of the flap. Studies that reported donor-site morbidities, including pain, hypoesthesia, or cold intolerance, are depicted in Table 2. The incidences of all donor-site morbidities are separately presented in Table 3.

Pain

The mean incidence of pain reported was 23% (SD 7.8) (see Table 3). Pain was either subjectively reported by the patient or measured using a visual analog scale (VAS) or Disability of the Arm, Shoulder, and Hand (DASH) score. In ten studies, a scale was used to measure pain severity; 17% of the patients scored a VAS of 4 or higher. Twenty studies (39%) investigated pain at the donor-site after harvest of the RFFF. In three studies, the location of pain was described along with the distribution of the RSN (15%). Other locations of pain in the remaining studies included the skin graft (15%), scar area (10%), or the distribution of the lateral antebrachial cutaneous nerve (LABCN) (5%). The majority of studies (55%) did not specify the location of the pain.

Hypoesthesia

The mean incidence of hypoesthesia amongst all patients was 34% (SD 25) (see Table 3). Locations of hypoesthesia included, amongst others, the area of the RSN (41%) and the skin graft area (14%). Hypoesthesia was mostly subjectively reported by patients through questionnaires, although some studies performed objective measurements, including Semmes-Weinstein monofilament testing to detect loss of sensation. Hypoesthesia was the most frequently reported donor-site morbidity, investigated by 73% of the studies. Yet, only nine studies elaborated on it by performing a 2-point discrimination (2PD) test to objectively assess the ability to discern two nearby objects on the skin of the
## Table 2  Donor site morbidities after FRFF

| Author, year | RFFF (n) | Pain reported by patient (%) | Pain score (assessment) | Nerve injury Hypoesthesia (%) | Neuropathic pain indication Cold intolerance (%) |
|--------------|---------|------------------------------|-------------------------|------------------------------|-----------------------------------------------|
| Bardsley et al., 1990 | 100 | - | 2.5/10 (VAS) | 17 | 5 |
| Bootz et al., 1991 | 51 | 14 | - | 31 | 14 |
| Brown et al., 1996 | 21 | - | - | 23 | - |
| Suominen et al., 1996 | 18 | - | - | 56 | 39 |
| Suominen and Asko, 1996 | 18 | - | - | - | 44 |
| Chambers et al., 1997 | 21 | 19 | - | 43 | - |
| Richardson et al., 1997 | 103 | - | - | 32 | 14 |
| Brown et al., 1999 | 11 | - | - | NS | - |
| Lutz et al., 1999 | 95 | - | - | 54 | 0 |
| Nehrer-Tairych et al., 1999 | 13 | - | - | 15 | 23 |
| Sidebottom et al., 2000 | 68 | NS | 1.3/100 (VAS) | - | - |
| Avery et al., 2001 | 25 | - | - | - | - |
| Nehrer-Tairych et al., 2002 | 35 | - | - | 20 | 9 |
| Sakai, 2003 | 9 | - | - | 22 | - |
| De Bree et al., 2004 | 37 | - | - | 46 | 16 |
| Huang et al., 2004 | 20 | - | - | 80 | NS |
| Chen et al., 2005 | 28 | - | - | 18 | - |
| Grinsell et al., 2005 | 51 | 18 | - | 36 | 18 |
| Ito et al., 2005 | 23 | - | - | 83 | - |
| Zuidam et al., 2005 | 34 | 21 | - | 26 | - |
| Ho et al., 2006 | 25 | - | - | - | - |
| Kerawala et al., 2006 | 50 | - | - | 76 | 24 |
| Rowe et al., 2006 | 23 | - | - | - | 27 |
| Selvaggi et al., 2006 | 125 | - | - | - | 0 |
| De Witt et al., 2007 | 50 | - | - | 22 | 8 |
| Karimi et al., 2007 | 41 | NS | 1.9/10 (VAS) | 36 | - |
| Novak et al., 2007 | 19 | 37 | - | 11 | 26 |
| Loreti et al., 2008 | 17 | - | - | 88 | - |
| Thiele et al., 2008 | 53 | - | - | 20 | 28 |
| Chang et al., 2010 | 12 | - | - | - | - |
| Morrissey et al., 2010 | 10 | NS | 16.9/20 (VAS) | 0 | - |
| Davis et al., 2011 | 47 | 22 | >3/10 (VAS) | 11 | - |
| Lee et al., 2011 | 19 | 26 | 0.5/10 (VAS) | 89 | - |
| Avery et al., 2012 | 60 | - | - | - | 30 |
| Jaquet et al., 2012 | 44 | - | - | NS | - |
| Sinclair et al., 2012 | 60 | 17 | - | 8 | - |
| Hekner et al., 2013 | 28 | - | - | - | 21 |
| Lane et al., 2013 | 45 | NS | 7.8/10 (VAS) | 42 | 16 |
| Lee et al., 2013 | 23 | - | - | 30 | - |
| Orlik et al., 2014 | 9 | - | - | NS | 44 |
| Schwarzer et al., 2016 | 50 | 18 | - | 56 | - |
| Foissac et al., 2017 | 20 | NS | 4.3/10 (VAS) | - | NS |
| Aslam-Pervez et al., 2018 | 12 | 17 | - | - | - |
| Pirlich et al., 2018 | 39 | 18 | - | - | - |
| Wang et al., 2018 | 31 | NS | - | NS | NS |
| Bertino et al., 2019 | 15 | NS | 5/20 (DASH) | - | - |
| Kansy et al., 2019 | 73 | 38 | - | 1 | 1 |
| Mashrah et al., 2019 | 13 | - | - | 62 | - |
| Potet et al., 2019 | 101 | NS | 1.1/10 (VAS) | 37 | - |
| Jani et al., 2020 | 52 | - | - | 40 | 2 |
| Krane et al., 2020 | 136 | - | - | - | - |

NRS = not specified, VAS = visual analog scale, DASH = Disability of the Arm, Shoulder and Hand, 2PD = 2-point discrimination, LTS = light touch sensation, STS = sharp touch sensation, SD = standard deviation
hand. Of these nine studies, 79% of the patients showed a reduction in two-point discrimination, indicating loss of sensation. The 2PD test was performed in the area of the RSN (50%), hand and fingertips (33%), or at the donor-site (17%).

Loss of sharp or light touch

Loss of light and sharp touch sensation were two of the fewest reported donor-site morbidities, investigated in eight and five studies, respectively. Of the few studies that investigated loss of sharp or light touch sensation, 28% of the patients reported a loss of light touch sensation, and 31% loss of sharp touch sensation. Both sharp and light touch sensation was measured in the RSN or skin graft area. Avery et al. measured light touch sensation with Semmes-Weinstein monofilaments between subfascial and suprafascial RFFFS. Light touch sensation in the thenar palm area was lower in the subfascial group, indicating injury to the thenar cutaneous sensory branches during dissection.  

Cold intolerance

Cold intolerance was reported in 13% (SD 13) of the patients and was investigated by 49% of all studies. Studies assessed the presence of cold intolerance through questionnaires. In addition, De Bree et al. found a minor decrease in the hand’s resting skin temperature on the operated side compared to the non-operated side.  

Hyperesthesia

Hyperesthesia is a positive sensory symptom that may occur through abnormal spontaneous or ectopic signals generated from damaged peripheral nerve fibers and is seen as an indicator for neuropathic pain. Eight studies reported the presence of hyperesthesia following harvesting of the RFFF, with a mean incidence of 16% (SD 15) (see Table 3).

Table 3 Incidence of donor site morbidities after RFFF

| Donor site morbidity | Incidence, % (SD) | Number of studies reported in, n (%) |
|----------------------|-------------------|--------------------------------------|
| Pain                 | 23 (7.8)          | 20 (39)                              |
| Mean VAS ≥4          | 17 (2.4)          | 10 (20)                              |
| Nerve injury         |                   |                                      |
| Hypoesthesia         | 34 (25)           | 37 (73)                              |
| Reduced 2PD          | 79 (36)           | 9 (18)                               |
| Light touch          | 28 (26)           | 8 (16)                               |
| Sharp touch          | 31 (31)           | 6 (12)                               |
| Neuropathic pain     |                   |                                      |
| Cold intolerance     | 13 (13)           | 25 (49)                              |
| Hyperesthesia        | 16 (15)           | 9 (18)                               |
| Neuroma              | 5 (4.6)           | 6 (12)                               |

Neuroma

Only six studies reported painful neuroma formation after harvesting of the RFFF. The examination of identifying neuroma formation was not specified in any of the studies. The neuroma location was described to be along with the distribution of the RSN (83%) or was not specified (17%).

Discussion

In this systematic review, 51 articles with a mean LOE of 3 were evaluated to determine the magnitude of the incidence of neuropathic pain and altered sensation in the donor-site following harvesting of the RFFF. The donor-site is often closed with a skin graft, making it prone to donor-site morbidities. Previous literature reported that 61% of the patients following RFFF harvest have complaints about cosmesis and sensibility in the hand.  

In this study, we found a mean incidence of 34% for hypoesthesia around the donor-site and a mean incidence of 23% for pain. Furthermore, hyperesthesia and cold intolerance were reported by 16% and 13% of the patients, respectively. Neuropathic pain is clinically characterized by spontaneous pain or evoked types of pain, including hyperesthesia and cold intolerance  

In the RFFF, iatrogenic nerve injury may trigger a consequence of molecular changes in nociceptive neurons that eventually become abnormally sensitive and develop pathological spontaneous activity.  

Of the 20 studies investigating pain at the donor-site, only one study specifically reported neuropathic pain; however, the authors did not elaborate on the difference between neuropathic pain and general pain.  

Furthermore, the development of true painful neuromas was reported by six studies, which reported a mean incidence of 5.0%. We believe this is an underestimation of the actual incidence of neuroma formation, as all neuromas were subjectively diagnosed by clinical presentation, and none were objectively diagnosed by a Tinel test. In addition, a minimum of only six studies included this in their analysis. Despite the scarce mentioning of explicit neuropathic pain, hyperesthesia, and cold intolerance, both indicators for neuropathic pain  

were more frequently described. Three studies elaborated on the origin of cold intolerance, and all three conclude that the cold intolerance does not seem to have a vascular cause, but instead is most likely a result of disturbances in the sympathetic nervous system.  

The relatively high incidences of hyperesthesia and cold intolerance may therefore indicate a higher incidence of actual neuropathic pain. Harvest of an RFFF bears the potential risk of iatrogenic nerve damage, which may eventually lead to the emergence of neuropathic pain. Several nerves are at risk for iatrogenic nerve damage, including the RSN and LABCN, and their anatomic variations increase the risk of iatrogenic nerve damage even further.  

Determining the exact source of neuropathic pain between these nerves, however, remains difficult. The RSN is at high risk to iatrogenic nerve damage due to its superficial location, especially during closure of the donor-site with a skin graft.  

However, even though the LABCN is almost always dissected during RFFF surgery, little to no studies report specific on damage of the LABCN and subsequent pain complaints. Solely one study in
This systematic review reported complaints alongside the distribution of the LABCN. The location and subcutaneous tissue at the dorso radial side of the wrist is probably more prone for adhesions and therefore neuropathic pain of the RSN is more likely compared to the LABCN. However, evidence that specifically the RSN is at the source of neuropathic pain has so far not been reported in the literature. Besides iatrogenic nerve damage during harvesting of closure, the skin graft may also be at the source of donor-site pain. A full-thickness graft (FTG) or split-skin graft (SSG) is used for donor-site closure that often overlies the nerves in this area, possibly instigating nerve irritation. A study by Pirlich et al. compared functional outcomes between donor-site closure with an FTG or direct closure; however, no substantial difference in pain incidences was found between the two techniques. Four studies used flaps for donor-site closure, including an anterolateral thigh flap\textsuperscript{19}, an ulnar-based transposition flap\textsuperscript{13}, a bilobed flap\textsuperscript{30,31}, and a keystone flap\textsuperscript{32}, however no considerable differences compared to skin graft closure were found. The difficulty in distinguishing the origin of donor-site pain between the different nerves or skin grafts emphasizes how little is known regarding this problem so far, and highlights the importance of investigating this in future studies.

Several techniques have been described to manage nerve injury during surgery and prevent neuropathic pain. Primarily, thorough identification of the RSN and its (multiple) branches can potentially minimize iatrogenic damage. Furthermore, neurectomy and burying the nerve in muscle or bone have shown to be proper prevention methods against neuropathic pain development.\textsuperscript{25,31} Newer techniques as targeted muscle reinnervation (TMR) seem to be effective techniques in reducing neuroma pain\textsuperscript{32,33}. The pronator quadratus and flexor digitorum profundus muscles have been suggested as primary muscle targets for the radial nerve\textsuperscript{34}, however, scientific evidence of this method to reduce neuropathic pain in the RSN area is still very limited. A study by Pet et al. evaluated targeted nerve implantation (TNI) to reduce neuroma pain in amputee patients.\textsuperscript{35} It showed that fewer patients experienced neuroma pain if TNI was performed preventively during primary surgery, compared to performing TNI during secondary surgery. Nonetheless, no studies have specifically investigated these more recent techniques, including TMR or TNI, in the RSN area yet.

The results of this systematic review should be interpreted in the context of its limitations. First, it is important to emphasize that the location of neuropathic pain complaints was not always specifically described to be along with the distribution of the RSN. The 20 studies that evaluated the presence of pain did not all limit nor specify pain to the area of the RSN. Three studies reported that pain developed in the distribution of the RSN, however, a majority of eleven studies did not specify the location of the pain. Therefore, it was not possible to distinguish the source of pain or hyposthesia between the RSN, LABCN, or skin graft area leading to the inability to perform an adequate meta-analysis. Second, a wide range of diagnostics was used in the included studies to identify donor-site morbidities, ranging from clinical observations to objective measurements. Therefore, it is likely that the reported incidence of donor-site morbidities is not very accurate. Finally, the majority of patients in this study were oncological patients who underwent RFFF surgery to cover the defect following tumor resection in the head and neck area. Most likely, the symptoms of neuropathic pain in the hand were inferior to the other medical problems that these oncological patients face. This may cause a lower reporting rate of neuropathic pain leading to an underestimation of its incidence.

This systematic review presents relatively high incidences of neuropathic pain indicators, suggesting that a substantial number of 23% of all patients deal with neuropathic pain symptoms following the harvest of an RFFF. So far, no clear incidences of neuropathic pain in the donor-site following RFFF have been described, even though clinical experience shows that patients often suffer from it. Clarifying the magnitude of this problem is of great relevance before elaborating on techniques to treat or prevent neuropathic pain in the donor-site, and this systematic review is the first to do so. We recommend proper attention to and accurate physical examination of the donor-site and areas along the RSN and LABCN distributions during follow-up appointments. Future studies should focus on determining the origin of neuropathic pain following RFFF harvest, and eventually on preventive measures to further improve the clinical outcomes of this widely used flap.

Disclosure
The authors have no financial interest to declare concerning the content of this article.

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Supplementary materials
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