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INTERVENTIONAL NEURORADIOLOGY

Osteoporotic vertebral compression fracture augmentation by injectable partly resorbable ceramic bone substitute (Cerament™|SPINESUPPORT): a prospective nonrandomized study

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Abstract
Introduction This study aimed to evaluate long-term stabilizing healing effectiveness and influence on adjacent intact vertebral bodies of a new injectable partly resorbable calcium sulfate (60 wt.%)/hydroxyapatite (40 wt.%) bone substitute employed in vertebral augmentation of osteoporotic collapses.
Methods From April 2009 to April 2011, 80 patients underwent vertebral augmentation. Patient enrolment criteria are as follows: age more than 20 years; symptomatic osteoporotic vertebral compression fracture from low energy trauma encompassing level T5 to L1 and classified as A1.1 to A1.2 according to the AO classification system; vertebral height compression within 0–75% compared to the posterior (dorsal) wall; client history confirming the age of the compression fracture to be within at least 4 weeks; and patients who are able to understand the procedure and participate in the study. Preoperative and postoperative imaging studies consisted of computed tomography, plain X-ray, dual X-ray absorptiometry scanning, and magnetic resonance. Pain intensity has been evaluated by an 11-point visual analog scale (VAS), and physical and quality of life compromise assessments have been evaluated by Oswestry Disability Questionnaire (ODI). All procedures have been performed fluoroscopically guided by left unilateral approach under local anesthesia and mild sedation.
Results VAS-based pain trend over 12-month follow-up has shown a statistical significant ($p<0.001$) decrease, starting from 7.68 (SD 1.83) preoperatively with an immediate first day decrease at 3.51 (SD 2.16) and 0.96 (SD 0.93) at 12 months. The ODI score dropped significantly from 54.78% to 20.12% at 6 months. None device-related complication has been reported. In no case, a new incidental adjacent fracture has been reported.
Conclusion Data show how this injectable partly resorbable ceramic cement could be a nontoxic and lower stiffness alternative to polymethylmethacrylate for immediate and long-term stabilization of osteoporotic collapsed vertebral bodies.

Keywords Osteoporosis · Vertebral fractures · Vertebroplasty · PMMA · Ceramic bone substitute

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Introduction

Vertebral compression fractures represent one of the most common complications of osteoporosis [1]. Their impact on quality of life (QoL) and mortality is huge because they lead to several complications sweeping from kyphotic deformities with respiratory involvement, to pain regardless of mobility, to mood changes [2–4].

Percutaneous vertebral body augmentation is a proven procedure for treatment of osteoporotic and pathologic acute vertebral compression fractures (VCFs) refractory to medical therapy and without neurologic deficits due to medullar/root involvement. The treatment has been shown to improve function in more than 85% of cases [5–9].

The most employed device for vertebral augmentation is polymethylmethacrylate (PMMA), first introduced in 1984, which assures optimal and potentially eternal vertebral stabilization with immediate pain reduction [10]. Some disadvantages are embedded in its mechanical and chemical characteristics, like high stiffness with possible altered vertebral body load transfer, monomer toxicity, and possible heat damage on surrounding soft tissues owing to exothermal setting polymerization [11–13].

The aim of this study is to verify if an alternative cement, Cerament™|SPINESUPPORT–BONESUPPORT AB, Lund, Sweden, with osteoconductive properties consisting of calcium sulfate and hydroxyapatite, may be effective for the scope of vertebral augmentation, i.e., immediate pain relief and fracture stabilization. The main advantages are fracture stabilization by bone remodeling and the lack of chemical and temperature effect on surrounding structures in case of leakages. Moreover, its bone-like stiffness may decrease the risk of adjacent level fractures.

Material and methods

Ethics

From April 2009 to April 2011, 80 patients with osteoporotic vertebral compression fractures undertook vertebral augmentation using a novel injectable and partly resorbable ceramic bone substitute. The study, a prospective non-randomized trial, was approved by our institution ethical committee and an informed consent was achieved before any study-related activity (vertebral augmentation, imaging studies, and follow-up test administration).

Patient selection

All patients were identified at our institution's outpatient department. Patients were enrolled if they met the following criteria: age more than 20 years; symptomatic osteoporotic vertebral compression fracture from low energy trauma encompassing level T5 to L1 and classified as A1.1 to A1.2 according to the AO classification system [14]; vertebral height compression within 0–75% compared to the posterior (dorsal) wall; client history confirming the age of the compression fracture to be within at least 4 weeks; and patients able to understand the procedure and participate in the study. Patients with known illness such as cancer, irreversible coagulopathy or bleeding disorder, preexisting calcium disorder (e.g., hypercalcemia), diabetes, and renal failure (dialysis) and also those presenting a compression fracture with retropulsed fragment or patients who had previously undergone vertebroplasty/kyphoplasty at the fracture site were excluded. Moreover, patients were considered not eligible if they presented infections or other skin damage at the puncture site, have history of anaphylactic reaction to iodine-based contrast media, and have a body mass index more than 30.

Clinical assessment and follow-up

A careful physical examination, including neurological examination, was conducted prior to the procedure to assess patients' clinical condition. During the screening investigation, use of painkillers was recorded. In most cases, patients who attended the screening session had a magnetic resonance imaging (MRI) exam performed elsewhere; in these cases, they undertook the scheduled first day MRI examination anyway. In all cases where patients attended the screening examination without an MRI exam, this was performed the day after at our institution, as part of the screening. MRI exams performed at our institution the day after the screening examination were not repeated on the first admittance day.

Patients who met the above criteria were scheduled to be treated as soon as possible according to our institution's daily bed availability; treatment in most cases took place 1 week later, and in four cases, it was 2 weeks later. Post-procedural physical examinations were scheduled at day 7 and at months 1, 6, and 12.

All patients were treated the day after hospitalization. During the admittance day, they undertook plain roentgengrams (X-ray), MRI if not performed at our institution the week before, and computed tomography (CT) of the spinal segment involved. Dual X-ray absorptiometry (DXA) scanning was performed the same day to assess osteoporosis [15]. Follow-up imaging investigations were scheduled as follows: plain X-ray, CT, and MRI at months 1 and 6; plain X-ray and CT at 12 months. To minimize patient radiation exposure during the four-step CT follow-up, post-procedural CT scans were confined to one segment above and one below the treated vertebral body.

Pain intensity was evaluated by an 11-point visual analog scale (VAS) administered before and after procedure at days 1 and 7 and at 1, 6, and 12 months. Physical and QoL compromise assessment was evaluated by Oswestry Disability Questionnaire (ODI) administered the day before procedure and at months 6 and 12 [16, 17].

Operational technique and device

All procedures were performed with patients in prone position under local anesthesia (lidocaine/bupivacaine 1%/0.25% for

skin incision; ropivacaine 10 mg/mL for periosteal anesthesia), with fluoroscopic guidance and in some cases supported by mild sedation. In all cases, the approach was transpedicular. The favorite approach was represented by the left unilateral approach, according to the habit of the first operators and good visibility of the bilateral pedicles cortical boundary. Our technique did not differ substantially from the standard well-established procedure described elsewhere [18]. To set an intravertebral cement spread as homogeneous as possible, the 13-gauge straight injection cannula was at first advanced up to the anterior third of the vertebral body (Fig. 1). Cement was gently injected paying careful attention to any leakage (intradiscal or intravenous); if it happened, injection was stopped for 3–4 min to allow partial cement hardening and then restarted. Once maximum cement spread was achieved at this site, the tip of the cannula was retracted to the posterior third, retrying cement injection. This two-step injection, in our experience, allowed us to achieve cement filling as complete as possible.

At the end of procedure, patients were kept for 20 min in prone position before rolling over into a bed where they were kept for 3 h in supine position before letting them free to the outpatient clinic. Because most patients used analgesic medications before hospital admittance, they were encouraged to terminate with these the following few days after procedure, and they were instructed to contact us in case of any discomfort. Patients, in absence of complications, were planned to be discharged the day after the procedure. CT scans targeted on the treated level were performed 5 to 8 h after procedure, to visualize cement spread and rule out fluoroscopy occult leakage.

The investigational device, CERAMENT™|SPINESUPPORT (CSS) is a CE-approved medical device intended for augmentation of vertebral compression fractures. It is an injectable and partially resorbable ceramic bone substitute. The device consists of synthetic calcium sulfate (60 wt.%) and hydroxyapatite (40 wt.%), mixed with the radiocontrast agent CERAMENT™|C-TRU (iohexol 300 mg iodine/mL). The device allows bone ingrowth after curing.

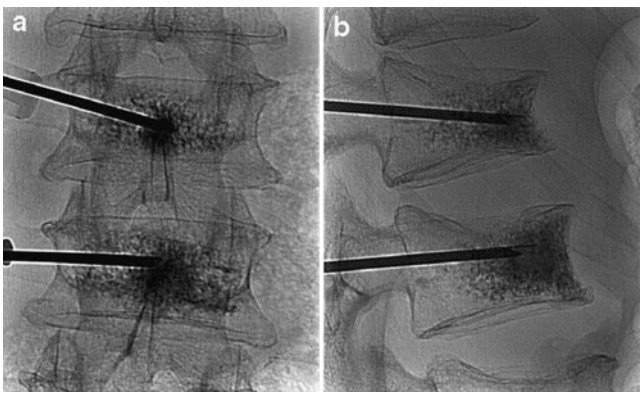

Fig. 1 Anteroposterior (**a**) and lateral (**b**) intra-procedural fluoroscopic view. Good cement impregnation showed by its good radiopacity

Statistical methodology

Data are presented as average, standard deviation, and significance level. Given the sample size (80 patients), raw data were recorded and analyzed on SAS™ statistical software by two-tailed matched-pair two sample *t* test. Differences in averages were accepted as significant at $p<0.001$.

Theory

The investigational device (CSS) is an injectable and partially resorbable ceramic bone substitute consisting of 60% synthetic calcium sulfate and 40% hydroxyapatite, mixed with the radiocontrast agent CERAMENT™|C-TRU (iohexol 300 mg iodine/mL). Once mixed, powder and liquid compose a viscous paste able to be easily injected (Fig. 2). During the complete hardening period (about 2 h), CSS becomes solid providing fracture mechanical stabilization. The calcium sulfate dehydrate component will be gradually resorbed allowing the implant to be remodeled through bone ingrowth [19]. The hydroxyapatite component remains intact for years providing an osteoconductive matrix for new bone ingrowing and long-term armoring of the osteoporotic vertebra. The components of CSS have been used in humans for decades and are proven to be highly biocompatible. The compressive strength of CSS is similar to cancellous bone, with the potential of minimizing the risk of implant-induced adjacent fractures [20–22].

Results

Eighty patients [47 (58.8%) women; 33 (41.2%) men] underwent vertebral augmentation. Patients' mean age was 66.12 (SD 14.28) years; male mean age was 65.18 (SD 14.21) years, and female mean age was 66.81 (SD 14.28) years. All female patients were osteoporotic

Fig. 2 CERAMENT™ is highly injectable and can be extruded through cannulae with a minimum inner diameter of 0.191

[mean DXA *T* score: proximal femur −2.98 (SD 0.19), lumbar spine −2.79 (SD 0.21)]. Forty-two women were already receiving therapy for osteoporosis; five women, not being under treatment yet, were scheduled at our institution's orthopedic department for appropriate treatment. DXA scans performed on males ruled out osteoporosis in 25 patients according to WHO cutoff [mean *T* score: proximal femur −2.73 (SD 0.20), lumbar spine −2.68 (SD 0.19)] [15, 23–26]. DXA scans performed at 1 year did not show statistical significant differences in *T* score values for both men and women.

An overall amount of 128 levels were augmented, 50 levels for men and 78 levels for women. Collapsed vertebral bodies showed a bimodal spinal segmental distribution with peak prevalence at the mid-thoracic and thoracic–lumbar junction, congruous with epidemiological data [27]. Data on level involvement for each patients were gathered as follows: 44 patients with a single collapse, 20 (25.00%) men and 24 (30.00%) women; 24 patients with double level involvement, 9 (11.25%) men and 15 (18.75%) women; and 12 patients with triple level involvement, 4 men (5.00%) and 8 (10.00%) women. Data on involved level contiguity for each patient were gathered as follows: 16 (20.00%) patients suffered a double contiguous vertebral collapse, 4 (5.00%) patients presented a double collapse with a healthy vertebral body in between "sandwich", 4 (5.00%) patients presented double distant collapse; 8 (10.00%) patients presented triple contiguous collapse, 3 (3.75%) patients presented a double contiguous plus a sandwich below collapse ($B_n-B_{n+1}-B_{n+3}$), and 1 (1.25%) patient presented three distant collapses. Data on fracture type (AO classification system) [14] were gathered as follows: 35 (27.34%) levels classified as A1.1 and 93 (72.66%) levels classified as A1.2. Type A1.2 fracture frequency was found significantly higher in women population and with multiple level involvement.

Bilateral transpedicular approaches were in no case necessary for optimal cement spreading and all procedures were performed through the left-sided pedicle. The mean volume of cement injected was 3.35 mL (SD 0.38), with 1.5–5 mL range. At targeted CT scans performed some hours after the procedure, cement leakages were reported in 15 levels (11.7%); nine (60%) of these were intradiscal and six (40%) were represented by small cement wedging inside the anterior venous plexuses. Thanks to the excellent cement radiopacity all intradiscal leaks had been immediately identified under fluoroscopy. Of nine intravenous wedging, only three were detected fluoroscopically, the remaining six being identified by CT scans.

At 1.5 month after procedure, in two single level cases, painful symptomatology suddenly arose again with same intensity and location as preoperative. Patients undertook extra-protocol MRI and CT scans. In both cases, CT scans were negative for unstable fracture, but in one case, MRI scans showed, at the treated level (L4), the typical signs of vertebral body edema just underneath the superior endplate, owing to a new collapse at the same level. This patient was retreated the day after MRI and re-followed up according to protocol. At 1 week, a six-point VAS drop was recorded; before the first treatment, VAS was 9, it dropped to 2 at 1-month follow-up, raised to 8 with the re-collapse, and eventually dropped to 2 to lay stable at the end of 1-year follow-up. In the patient with both negative CT and MRI exams, a persistent spasm of paravertebral muscles around the treated level was identified and promptly resolved in some days with analgesic drugs and thiocolchicoside.

VAS-based pain trend over the one-year follow-up showed a statistical significant decrease at both baseline and each interval comparison, starting from 7.688 (SD 1.825) points baseline score with an immediate first day decrease at 3.513 (SD 2.158) points, to get through 2.363 (SD 1.577) points at day 7, 1.875 (SD 1.247) points at day 30, 1.325 (SD 0.883) points at 6 months to end at 0.963 (SD 0.934) points at 1 year. Quality of life assessment sampled by ODI scoring also showed a statistical significant improvement with a baseline mean score of 54.78% (SD 15.82%) dropped at 22.61% (SD 8.35%) at 6 months to end with 20.12% (SD 11.53%) at 1 year. All significance levels for both VAS and ODI evaluation showed $p<0.0005$ (Figs. 3 and 4).

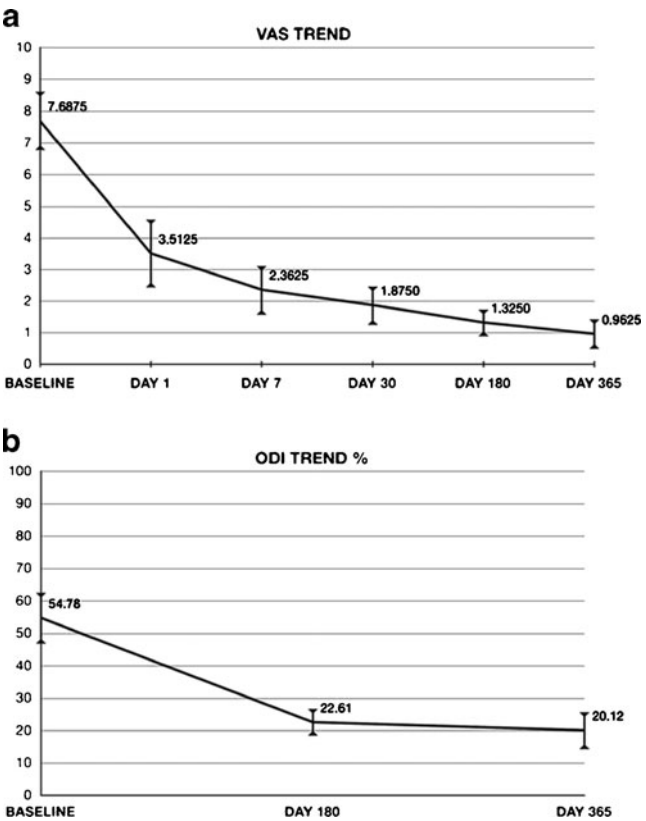

Fig. 3 Both VAS values (**a**) and ODI values (**b**) show a significant constant improvement over 12-month follow-up

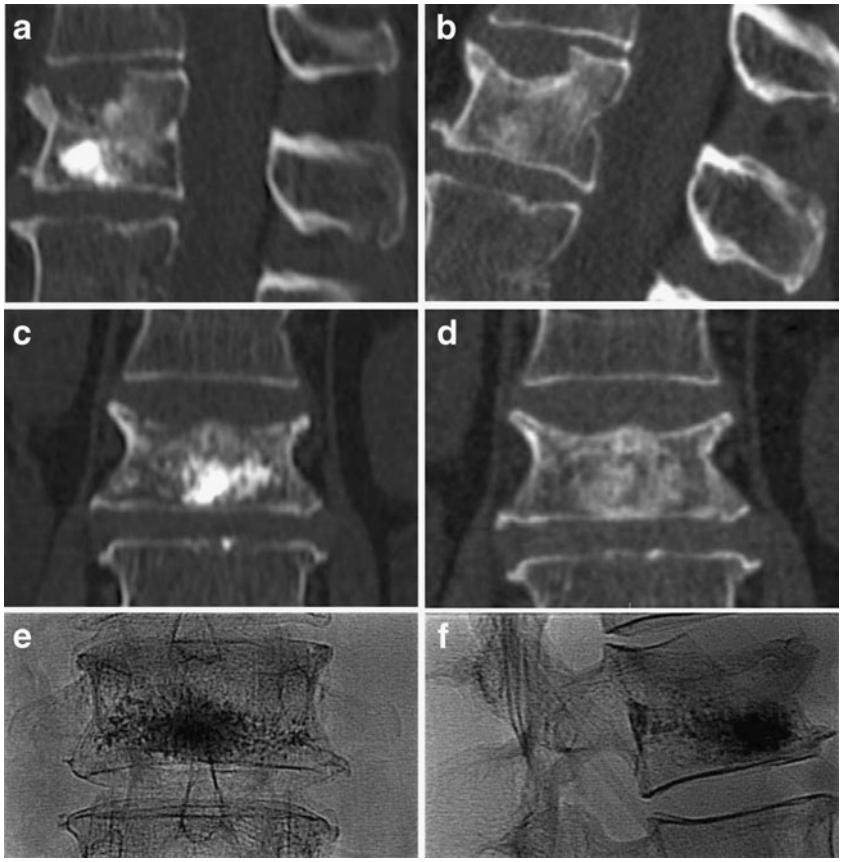

Fig. 4 CT scans of CSS spread inside collapsed vertebral body. Sagittal (**a**) and coronal (**c**) views at first day after the procedure. **b**, **d** appearance at 6 months, when iodine is completely resorbed and calcium sulfate should also be too. Anteroposterior (**e**) and lateral (**f**) fluoroscopic view of the same vertebral body

No intraprocedural or periprocedural complications were reported, except the small mentioned cement leaks. At the end of the one-year follow-up, no cases of new adjacent vertebral fractures were reported. In four cases (all women) with mono-level involvement, a new incidental fracture per person occurred at a distant level. The first early vertebral collapse occurred 7 months after procedure, the last at 9 months; all four cases were augmented by traditional PMMA cement vertebroplasty.

Discussion

Essentially pain and kyphotic deformities account for the great variety of life-threatening complications that follow the loss of mobility [28–30]. Vertebral augmentation is a technique of proven efficacy, almost immediately reducing pain related to osteoporotic and pathologic acute VCFs, with great improvement in patients' clinical condition and improvement in QoL [5–7, 9, 31].

PMMA is the most employed commercially available device for vertebral augmentation. Its proven effectiveness in reducing pain from vertebral collapse almost immediately is considered to reside not only in its fracture stabilizing action, but also in the secondary local nerve damage as a consequence to its high setting temperature and chemical toxicity. The available scientific literature data on PMMA setting-induced heat–chemical toxicity damage on surrounding nerve structures may be ambiguous [11–13, 32]. However, data on its mechanical and bone integration properties are clear. PMMA Young's modulus (1.8–3.1 GPa) is significantly higher than normal bone, thus interfering mechanically with the load stresses and preventing surrounding bone remodeling; in case of osteoporotic bone, PMMA strength is 8 to 40 times higher [33–37]. Such high stiffness may account for the risk of re-collapse of the spared, not impregnated, cancellous bone of the same vertebral body and for the risk of incidental adjacent fractures.

Complete cancellous bone impregnation, bridging both endplates and the axial level, appears to strengthen the whole vertebral body, reducing the risk of intra-somatic re-collapse. Additionally, such complete cement distribution may also affect adjacent vertebral body load transfer, potentially decreasing the risk of new incidental collapses, especially in "sandwich" vertebral bodies [38–41]. It was on the base of these hypothesis, and based on Cerament's lower stiffness (0.3–0.4 GPa), which is comparable to normal trabecular bone, that we strived for a complete vertebral body cement filling.

The rationale of the ideal bone substitute lies in its ability to be resorbed at a rate equal to new bone ingrowth, achieving complete bone remodeling and healing, while being able

to tolerate the motion–load stresses the spine usually undergoes. With calcium sulfate alone, strength is too weak, compared to that of cancellous bone and its rate of resorption is too high to allow new bone ingrowing. Cerament consists of calcium sulfate and hydroxyapatite; the hydroxyapatite acts as slow or never absorbable framework that slows down the absorption rate of calcium sulfate and at the same time act as an osteoconductive template for new bone ingrows. The hydroxyapatite particles are completely embedded inside new bone tissue during the new bone ingrowth. The mechanical properties, the low stiffness of the device, and the bone-remodeling processes decrease the shear stresses at the border bone/CSS [20, 22, 42–45].

In the study, one patient presented with a re-collapse of the already augmented vertebral body (L4) about 1.5 month after treatment. In this patient, there was no new trauma or any intradiscal leak from the first augmentation. The etiology of this occurrence could be explained by a combination of irregular cement filling and the lower mechanical strength of the device in the early stages of integration, when calcium sulfate resorption was still in progress and new bone ingrowing was limited [42]. Anyhow, once reaugmented with CSS, the painful symptomatology decreased, becoming equal to the mean of the other patients.

The involved vertebral bodies in our patients showed the typical "load stress"-related cluster distribution, with higher frequencies of collapses at mid-thoracic and thoracic–lumbar junction [46–49]. We were worried by the risk of adjacent fractures in sandwich vertebral body fractures. However, based on the above considerations and on the evidence presented by some authors [46, 50] showing the incidence of a vertebral collapse to be unaffected by the augmentation of the adjacent levels, we withstood from any preventively treatment.

Same authors argued that the frequency of adjacent vertebral fractures increases in case of intradiscal leakages [48]. In our study, we reported nine cases of such leakages, but none of these patients presented with new incidental adjacent or distant collapse in the 1-year follow-up. Four women with mono-level involvement presented a new collapse at distant levels.

According to our data, immediate fracture stabilization and pain relief, assessed by imaging and VAS score, were completely accomplished by augmentation with this device. Also the QoL, as assessed by ODI score, showed significant improvement.

Follow-up showed immediate and lasting pain relief in absence of new incidental fractures and no device-related adverse reactions. Our results strongly suggest that CSS can be an effective alternative to PMMA. We propose that the sustained pain relief during the 12-month follow-up period is due to new bone ingrowth, and this is supported by another study on osteoporotic patients undergoing wrist osteotomy augmentation with the same device, showing its complete substitution by new bone [22]. However, in this study, it was not possible, for ethical reasons, to investigate on long-term bone device integration by biopsy samples.

Conclusions

CERAMENT™|C-TRU, a new bioactive calcium sulfate/hydroxyapatite cement for vertebral augmentation, has shown immediate and long-term effectiveness leading to immediate and lasting pain relief, improved QoL, and absence of any device-related complication, including new incidental adjacent fractures.

Conflict of interest We declare that we have no conflict of interest.

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