Ultra low-dose naloxone and tramadol/acetaminophen in elderly patients undergoing joint replacement surgery: A pilot study

Ngozi N Imasogie FRCA(UK), Sudha Singh FRCP, James T Watson FRCP,
Debbie Hurley RN, Patricia Morley-Forster FRCP

OBJECTIVE: A pilot study was conducted to assess whether both the rationale and feasibility exist for future randomized clinical trials to evaluate the combined use of naloxone infusion and tramadol/acetaminophen as opioid-sparing drugs in elderly patients undergoing lower extremity joint replacement surgery.

DESIGN: Ten patients 70 years of age or older undergoing either total knee (n=7) or total hip (n=3) arthroplasty were treated prospectively. Each patient received two tablets of tramadol/acetaminophen (Tramacet; Janssen-Ortho Inc, Canada) preoperatively and every 6 h postoperatively, as well as a naloxone infusion started preoperatively at 0.25 µg/kg/h and continued up to 48 h postoperatively. In addition, standard intraoperative care was provided with 0.2 mg of intrathecal morphine, 1.4 mL of 0.75% bupivacaine, and an intra-articular infiltration of 100 mL of 0.3% ropivacaine and 30 mg of ketorolac, as well as standard postoperative morphine via patient-controlled analgesia orders and celecoxib 200 mg twice daily for five days.

OUTCOME MEASURES: Compared with seven historical controls, also 70 years of age or older, who had undergone either a total knee (n=4) or total hip (n=3) arthroplasty, postoperative opioid use was reduced by 80%.

CONCLUSION: Consequently, a randomized, double-blinded clinical trial comparing standard therapy versus standard therapy plus these two drugs seems warranted. In such a trial, it would require approximately 20 subjects per treatment arm to detect a 80% decrease in morphine use.

Key Words: Analgesia; Elderly; Naloxone; Opioid-sparing; Total hip arthroplasty; Total knee arthroplasty; Tramacet; Tramadol

At present, opioids are the mainstay of postoperative analgesia, despite their numerous side effects. These side effects include respiratory depression, sedation, nausea, vomiting, pruritus, urinary retention, ileus and constipation. Frequently, these side effects require treatment with other medications, such as dimenhydrinate and diphenhydramine. However, both these medications and some opioids have been noted to demonstrate anticholinergic activity (1). In patients 70 years of age and older, anticholinergic medications have been associated with delirium and postoperative cognitive dysfunction, causing delays in discharge from hospital, as well as delays returning to independent living (2-4).

As the geriatric population of North America increases, more patients requiring surgery are 70 years of age and older (3). Therefore, it is important that alternate means of analgesia are found that limit or even eliminate opioid use.

Tramacet (Janssen-Ortho Inc, Canada) is a combination of two drugs – 37.5 mg tramadol and 325 mg acetaminophen – in a single oral tablet. This combined tablet has been used successfully in elderly patients to provide pain relief from arthritis (5).
Tramadol is a centrally acting analgesic with two distinct mechanisms of action. It is a weak opioid agonist and an inhibitor of monoamine neurotransmitter uptake. It is comprised of two enantiomers that act synergistically to produce analgesia. The analgesic potency ratio of morphine to tramadol is thought to range from 1:10 to 1:15 (i.e., 10 mg to 15 mg of tramadol provides the same degree of analgesia as 1 mg of morphine) (6-9).

Naloxone, an established mu (µ) antagonist, has been demonstrated to exert an opioid-sparing effect when it is administered as an ultra low-dose infusion (10,11). Because tramadol causes less respiratory depression and fewer sedative effects than morphine (6), and because it has been shown to be well tolerated and reduce opioid requirements in some settings when used in combination with them, it was hypothesized that tramadol/acetaminophen combined with an ultra low-dose infusion of naloxone may be a well tolerated and highly effective analgesic regimen in the postoperative period.

Consequently, the purpose of the present study was to assess whether both the rationale and feasibility exist for future randomized clinical trials (RCTs) to evaluate the combined use of naloxone infusion and tramadol/acetaminophen as opioid-sparing agents in elderly patients undergoing lower extremity joint replacement surgery. Rationale to pursue a future RCT would be determined by assessing whether the combined use of low-dose naloxone and tramadol/acetaminophen results in any clinically significant reduction, of at least two-thirds, in postoperative supplemental opioid use in experimental subjects versus historical controls (HCs). Feasibility would be determined by assessing the frequency and severity of side effects, such as nausea, vomiting, oversedation, respiratory depression, pruritus and confusion (6); estimating the sample size needed per treatment arm to detect a 67% reduction in opioid use in treated versus control subjects; and identifying any other problematic issues with such a trial.

METHODS

Before the initiation of data collection, the protocol was approved by the University of Western Ontario Research Ethics Board for the Review of Health Sciences Research Involving Human Subjects. Subjects were recruited consecutively from the list of patients scheduled for either total hip arthroplasty (THA) or total knee arthroplasty (TKA) at St Joseph’s Health Care Centre (London, Ontario) over a six-month period. To be eligible for inclusion in either the experimental subject or HC group, an individual needed to satisfy the following inclusion criteria: be 70 years of age or older at the time of surgery, have an American Society of Anesthesiologists (ASA) physical status score of 1 to 3, be able and willing to provide informed, written consent, and be able to communicate in English. Exclusion criteria were known allergies or contraindications to naloxone, tramadol, acetaminophen, nonsteroidal anti-inflammatory drugs, sulpha drugs or local anesthetics; any contraindication to spinal anesthesia; any contraindication to the use of celecoxib; chronic opioid use or abuse; and any chronic pain syndrome other than the indication for single joint replacement.

Because the present study was a pilot study, an a priori decision was made to recruit 10 subjects for the prospective arm of the study; roughly 50% were TKA patients and the remainder were THA patients. All patients in both the prospective and retrospective arms of the study received regional anesthesia and standard multimodal analgesic as per standard practice at St Joseph’s Health Care Centre, which included a subarachnoid block with 0.2 mg of epidural morphine and 1.4 mL of 0.75% bupivacaine, and a periarticular infiltration with 111 mL of a local anesthetic solution containing 300 mg of ropivacaine, 30 mg of ketorolac and 250 µg of adrenaline. Postoperatively, 200 mg oral celecoxib was given to patients twice daily for five days as per institutional standard practice. As well, morphine patient-controlled analgesia (PCA) set at 1 mL, with a delay of 6 min, no basal rate and a limit of 10 mL/h, was provided as a rescue analgesic to all patients. Above and beyond standard practice, each experimental subject received a low-dose naloxone infusion, started in the operating room, that ran at 0.25 µg/kg/h, and was continued for the duration of the patient’s hospital stay (an equivalent of 400 µg over 24 h in a 70 kg man), to be discontinued 1 h before patient discharge; and oral tramadol/acetaminophen (37.5 mg of tramadol plus 325 mg of acetaminophen), two tablets preoperatively, followed by two tablets every 6 h for five days postoperatively. Thereafter, experimental subjects were allowed one to two tablets of tramadol/acetaminophen as needed, never to exceed a total of eight tablets per day.

Data collection (every 6 h) included the recording of vital signs, global pain severity and other postoperative symptoms, and the amount of morphine used. In addition, a visual analogue scale (VAS) was used to quantify pain severity. The Ramsay sedation score (12) and the Mini Mental State Examination (MMSE) (13) were used to formally assess patients for degree of sedation and confusion, respectively, every 6 h throughout the postoperative hospital stay. For purposes of analysis, each day’s highest VAS pain severity and Ramsay sedation scores were used, and the lowest MMSE score.

HCs had received the multimodal analgesic regimen previously described as the standard for St Joseph’s Health Care Centre.

Data analysis

Mean daily morphine or morphine equivalent use, as well as variance, was calculated for both the prospective experimental subjects and the HCs. To analyze the data, it was assumed that mean daily morphine use would be non-normally distributed. Intergroup means were compared by nonparametric, two-tailed analysis using Wilcoxon’s signed rank test, with P<0.05 set as the threshold for statistical significance.

TABLE 1
Baseline characteristics of experimental and control subjects

| Baseline characteristics | Experimental subjects (n=10) | Historical controls (n=7) |
|--------------------------|-----------------------------|--------------------------|
| Men, n (%)               | 6 (60)                      | 3 (43)                   |
| Mean age, years          | 77.3                        | 75.7                     |
| Median age, years        | 75.5                        | 75                       |
| Age range, years         | 72–83                       | 70–81                    |
| TKA, n (%)               | 7 (70)                      | 4 (57)                   |
| Mean preoperative ASA    | 2.2                         | 2.9                      |

ASA American Society of Anesthesiologists; TKA Total knee arthroplasty
RESULTS

Final analysis consisted of 10 experimental subjects and seven HCs (Table 1). Demographically, the two groups were similar, with 70% of the experimental subjects (seven of 10) and 57% of the HCs (four of seven) having undergone TKA versus THA. Sixty per cent of the experimental subjects were men, versus 43% of HCs. The mean age, median age and age range were 77.3 years, 75.5 years and 72 to 83 years, respectively, in the experimental subjects, and 75.7 years, 75 years and 70 to 81 years, respectively, in the HCs. The mean preoperative ASA score was 2.2 among the experimental subjects (eight ASA scores of 2, two ASA scores of 3) versus 2.9 (one ASA score was 2.2 among the experimental subjects (eight range 0 mg/day to 15.3 mg/day) versus 24.9±17.9 mg/day in the HCs (P=0.25) – a difference that represented an 80% reduction in daily morphine dose (Table 2). The subjects were subdivided by procedure (TKA versus THA); among the seven experimental subjects and four HCs who underwent TKA, the mean number of morphine equivalents administered in the experimental subject group was 5.6±5.4 mg/day versus 30.9±19.4 mg/day in the HCs (an 82% reduction; P<0.03). Among the three patients in each group who underwent THA, the mean number of morphine equivalents administered in the experimental subject group was 3.8±3.4 mg/day versus 17.0±15.1 mg/day in the HCs (a 78% reduction; P=0.51, not significant).

VAS pain severity scores were highest on postoperative day 1 (Table 3 and Figure 1). Seven of 10 experimental subjects had a day 1 VAS score of 40 mm or lower at rest, while two of 10 had a day 1 VAS of 40 mm or lower on movement. All VAS pain scores on day 2 and day 3 at rest were lower than 40 mm. Five patients had VAS pain severity on day 2 of 40 mm or lower on movement, and by day 3, eight of 10 patients had achieved a VAS of 40 mm or lower on movement. Only one patient reported a VAS pain severity of 100 mm on movement on day 3, but the same patient reported no pain (0 mm) at rest. VAS pain severity scores were not available for the HCs due to their retrospective nature.

No significant sedation occurred in any of the patients (all Ramsay sedation scores = 0) (Table 3). Similarly, there were no episodes of mental confusion; of 28 MMSE scores, there were 23 scores of 30/30, three scores of 29/30 and two scores of 28/30 (mean MMSE score 29.7±0.6). None of the experimental subjects experienced any respiratory depression. Two patients had episodes of diaphoresis not associated with lightheadedness or syncope. Nausea occurred in 40%, emesis in 20%, and pruritus in 10%; all episodes of nausea and vomiting were transient. Brief episodes of diaphoresis occurred in two patients. No patients had to be dropped from the study protocol or have any treatment interrupted or discontinued due to untoward effects.

Independent ambulation was noted earlier than expected in the experimental subject group by the physiotherapist. When getting out of bed for the first time on postoperative day 1, some patients sat up and carefully swung their legs to the side of the bed (knees at 90°) without any help or complaints of pain. By early postoperative day 2, experimental subjects were ambulating with walkers only. Two of 10 experimental subjects were discharged on the third hospital day, and six on the fourth day. Two patients required longer hospital stays – one patient was anemic and suffered from congestive cardiac failure following a blood transfusion; the other patient’s discharge was delayed until placement in a convalescent home was possible. Neither delay was attributed to medication or level of pain.

To estimate sample size for the larger study, pooled variance was used, which was 143.0. Assuming a 20% dropout rate and a normal distribution for daily morphine dose (a reasonable assumption in a larger study), the calculation estimating the number of subjects needed to detect a reduction by two-thirds (67%) in the daily morphine dose within the context of a RCT yielded 19.2, which should be rounded up to 20 subjects per treatment arm.

DISCUSSION

In the present pilot study, the combination of an ultra low-dose infusion of naloxone plus oral tramadol/acetaminophen resulted in an 80% reduction in morphine use compared with morphine use observed in seven HCs. This highly clinically significant reduction in opioid use was achieved with no episodes of oversedation, somnolence, confusion or respiratory depression. Nausea occurred in 40%, emesis in 20%, and pruritus in 10%; all episodes of nausea and vomiting were transient. Brief episodes of diaphoresis occurred in two patients. No patients had to be dropped from the study protocol or have any treatment interrupted or discontinued due to untoward effects.

Naloxone is a narcotic μ antagonist that is normally used to reverse the respiratory depressant and sedative effects of opioids. Over the past few years, palliative care physicians have given oral opioid antagonists concurrently with opioids on a regular basis to reverse constipation, diaphoresis and other unwanted effects of high-dose opioids (14,15). In the postoperative setting, ultra low-dose naloxone infusion has been shown to have an analgesic effect, both in animal models (16,17) and in human patients (10,18). In a study intended to define the optimum dose of naloxone, Gan et al (10) found that an infusion of 0.25 µg/kg/h was associated with reduced opioid requirements

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**TABLE 2**

| Outcome | Experimental subjects | Historical controls | P | Opioid use reduction (%) |
|---------|-----------------------|---------------------|---|-------------------------|
| All subjects | n=10 | n=7 |  | 0.25 | 80 |
| Morphine equivalents, mg/day, mean | 5.1 | 24.9 |  |  |  |
| Morphine equivalents, mg/day, range | 0–15.3 | 0–56.0 |  |  |  |
| TKA | n=7 | n=4 |  | 0.03 | 82 |
| Morphine equivalents, mg/day, mean | 5.6 | 30.9 |  |  |  |
| Morphine equivalents, mg/day, range | 0.4–15.3 | 0–56.0 |  |  |  |
| THA | n=3 | n=3 |  | 0.51 | 78 |
| Morphine equivalents, mg/day, mean | 3.8 | 17.0 |  |  |  |
| Morphine equivalents, mg/day, range | 0–6.7 | 0–22.0 |  |  |  |

THA Total hip arthroplasty; TKA Total knee arthroplasty
and a reduction in adverse effects in patients undergoing total abdominal hysterectomies. Similarly, in an open-label study, Gordon et al (18) found that the combination of low-dose naloxone and nalbuphine resulted in good pain control and no significant adverse events after gynecological surgery, with some patients requiring no rescue medication (either morphine or fentanyl) at all. Moreover, in a rabbit model, Bergman et al (17) found that low-dose naloxone enhanced buprenorphine in a tooth pulp antinociceptive assay.

How can an opioid antagonist produce analgesia? One empirically supported explanation is that the body’s normal response to pain is to produce endorphins, which bind to opioid receptors in the brain to bring about analgesia. The release of enkephalin (an endorphin) is governed by a presynaptic autoregulatory system. Large quantities of enkephalins result in negative feedback, reducing further release. Naloxone, delivered as an ultra low-dose infusion, blocks this negative feedback, resulting in enhanced analgesia from enkephalins (10,11,16). Therefore, its effect may be antipronociceptive.

Tramadol is a centrally acting drug that exerts its analgesic effects through opioid (mainly µ) receptors, as well as through nonopioid receptors. It consists of two enantiomers, a (+) enantiomer and a (–) enantiomer. The (+) enantiomer is responsible for opioid activity and the (–) enantiomer has less opioid µ receptor affinity. The nonopioid activity of tramadol occurs by means of inhibition of the presynaptic uptake of monoamine neurotransmitters, such as noradrenaline and serotonin. Concentrations of noradrenaline and serotonin increase, inhibiting pain perception in pain-inhibitory pathways (5,19).

Tramadol already is being used alone as a potential opioid-sparing agent in the perioperative period. For example, Vickers and Paravinci (20) used 100 mg of intravenous tramadol as an initial dose with subsequent doses of 50 mg, providing up to 250 mg in the first 90 min and 650 mg in the first 24 h in abdominal surgery patients. Coetzee and van Loggerenberg (21) administered 188 mg of intravenous tramadol in the first 90 min following abdominal hysterectomy to achieve adequate analgesia; using an initial dose of 3 mg/kg body weight and titrating as necessary, they were able to eliminate the use of traditional opioid analgesics. We were unable to eliminate morphine from the analgesic regimen in our study, likely because we were limited in the quantity of tramadol we could offer patients; intravenous tramadol is not yet available in Canada. The maximum amount of tramadol we were able to administer, in the form of Tramacet, was 300 mg every 24 h.

Although tramadol is considered to be opioid sparing, the combination of morphine and tramadol, when used following abdominal hysterectomies, appears to be infra-additive, rather than additive or synergistic (22). Webb et al (23), in a study of

| Subject | Age, years | Sex | Surgery | LOS | VAS score, day 1, mm | VAS score, day 2, mm | VAS score, day 3, mm | Mean ME dose, mg/day | RSS, day 1/2/3 | MMSE, day 1/2/3 |
|---------|------------|-----|---------|-----|--------------------|---------------------|---------------------|-------------------|----------------|---------------|
| 1       | 82         | F   | TKA     | 7   | 0–10               | 10–30               | 10–30               | 0.4               | 0/0/0          | 30            | 30/30/30      |
| 2       | 80         | M   | TKA     | 3   | 40–60              | 15–41               | home                | 3.0               | 0/0/home       | 30            | 29/29/home    |
| 3       | 75         | F   | TKA     | 3   | 22–84              | 13–40               | home                | 15.3              | 0/0/home       | 30            | 30/30/30      |
| 4       | 81         | M   | TKA     | 3   | 0–65               | 0–90                | 0–30                | 1.7               | 0/0/0          | 30            | 30/30/30      |
| 5       | 83         | F   | TKA     | 6   | 30–90              | 0–10                | 0–100               | 3.0               | 0/0/0          | 27            | 29/28/28      |
| 6       | 76         | M   | TKA     | 3   | 15–70              | 20–30               | 10–30               | 10.0              | 0/0/0          | 30            | 30/30/30      |
| 7       | 72         | M   | TKA     | 4   | 65–70              | 10–55               | 3–30                | 6.5               | 0/0/0          | 30            | 30/30/30      |
| 8       | 75         | M   | THA     | 4   | 26–55              | 19–46               | 10–43               | 4.8               | 0/0/0          | 30            | 30/30/30      |
| 9       | 74         | F   | THA     | 4   | 70–90              | 5–46                | 15–34               | 6.7               | 0/0/0          | 30            | 30/30/30      |
| 10      | 75         | M   | THA     | 4   | 0–25               | 0–25                | 0–11                | 0                 | 0/0/0          | 30            | 30/30/30      |

F Female; LOS Length of hospital stay in days; ME Morphine equivalent; MMSE Mini Mental State Examination; Preop Preoperative; RSS Ramsay sedation score; THA Total hip arthroplasty; TKA Total knee arthroplasty; VAS 100 mm visual analogue scale

**Table 4**

| Subject | Age, years | Sex | Surgery | Complications |
|---------|------------|-----|---------|---------------|
| 1       | 82         | F   | TKA     | Dizziness, anemia, CHF post-transfusion |
| 2       | 80         | M   | TKA     | Nausea (day 0) |
| 3       | 75         | F   | TKA     | None |
| 4       | 81         | M   | TKA     | Nausea, emesis (day 0) |
| 5       | 83         | F   | TKA     | None |
| 6       | 76         | M   | TKA     | Nausea, emesis (day 0) |
| 7       | 72         | M   | TKA     | Nausea (day 2) |
| 8       | 75         | M   | THA     | Diaphoresis |
| 9       | 74         | F   | THA     | Leg hematoma, allergy, LOC |
| 10      | 75         | M   | THA     | Diaphoresis, pruritus (day 0) |

CHF Congestive heart failure; LOC Loss of consciousness; M Male; THA Total hip arthroplasty; TKA Total knee arthroplasty
69 laparotomy patients, compared morphine PCA alone to tramadol plus morphine PCA. They identified a significant reduction in morphine use in the tramadol group, amounting to a 52% reduction by the second postoperative day. The side effect profiles for the morphine group and the tramadol plus morphine group were similar; both had a low incidence of nausea, vomiting and sedation, and no respiratory depression. A possible explanation for this delay in opioid-sparing effect is that the M1 metabolite of tramadol (O-desmethyl tramadol) has greater opioid receptor affinity and twice the elimination half-life of the parent compound.

Excessive sweating, a known effect of tramadol, occurred in two of our patients. However, other adverse effects usually associated with opioid use (such as respiratory depression, somnolence and sedation) did not occur. One possible explanation for this is that the low-dose naloxone actually reduced the severity and incidence of side effects associated with morphine PCA, as has been shown elsewhere (24).

Several previous studies (9,22,23) have shown that morphine and tramadol cause nausea and vomiting to a similar degree. Other studies (25,26) have revealed higher rates of nausea and vomiting associated with tramadol; however, in these latter studies, tramadol was administered via bolus doses, whereas Webb et al (23) administered the tramadol via a continuous infusion. We noted a relatively high incidence of nausea and vomiting, perhaps because oral administration may mimic bolus administration, whereby high blood levels are attained within 30 min (time to effect). Tramadol does not cause respiratory depression, unlike morphine (9,22,23).

At St Joseph's Health Care Centre, hip and knee arthroplasty patients are usually home by the fourth postoperative day. Two of our study patients stayed longer than four days, one due to congestive heart failure that developed after a blood transfusion for anemia, and the other pending placement in a convalescent home. Nonetheless, our impression was that recovery was more rapid in the patients who received naloxone plus tramadol/acetaminophen than in the patients we usually observe, demonstrated mostly by earlier ambulation and better initial range of motion than we usually see in such patients.

Clearly, our study has limitations, largely because it was always intended to be a pilot study. We had only 10 'treated' subjects and seven HCs, and only six of our 17 patients underwent a THA, versus 11 patients who underwent a TKA. The mean ASA status of the HCs was also lower. Perhaps the most important limitation, however, was that we used HCs, for whom some data (such as daily VAS pain severity scores) were lacking, and who may have been treated somewhat differently outside the context of a study. Nevertheless, we believe that the dramatic 80% reduction in morphine use we observed, with the combination of ultra low-dose naloxone plus oral tramadol/acetaminophen warrants both reporting and a closer look, within the context of a double-blinded RCT comparing standard therapy with standard therapy plus this new drug combination. Conceivably, one even could argue for including third and fourth treatment arms, including standard therapy plus tramadol/acetaminophen alone, and standard therapy plus low-dose naloxone alone, although this clearly would double the size of the study, perhaps with little actual gain. Such a study certainly seems feasible, given that we observed no serious adverse reactions, and the variance in morphine equivalent dose we observed was small enough to justify only 16 to 20 subjects per treatment arm, depending on the dropout rate. In addition, even though we identified a statistically significant difference in our TKA patients, but not in our THA patients, we believe that this is an anomaly born out of the very few THA patients we had, rather than a true difference between the procedures. Note that the absolute reductions in morphine use were 82% and 78% in TKA versus THA patients, respectively; there is hardly a clinically meaningful difference between them.

CONCLUSION

These preliminary results hold great promise for the use of low-dose naloxone plus tramadol/acetaminophen as opioid-sparing agents in patients 70 years of age or older undergoing TKA or THA; certainly, a future RCT seems both warranted and feasible.

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APPENDIX

To determine the feasibility of a future RCT, we recorded the percentages of presumed drug-related side effects, as well as the number of subjects required to discontinue either naloxone ortramadol/acetaminophen or otherwise be dropped from the study protocol. We then estimated the per-treatment-arm sample size required to detect a two-thirds (67%) reduction in morphine use versus standard care, assuming a 20% dropout rate. To achieve the latter, we used the following formulas:

\[
N = \left(\frac{2(Z_{\alpha} + Z_{\beta})^2 \sigma^2}{\Delta^2}\right)
\]

\[
N_{0.80} = \frac{N}{0.80}
\]

Within the formulas, \(N\) = the subjects needed in each treatment arm of a two-arm study with equal samples in each; \(Z_{\alpha} = 95%\) confidence = 1.96; \(Z_{\beta} = 90%\) power = 1.64; \(\sigma^2\) = the variance in the daily morphine equivalent dose, expressed in mg; \(\Delta\) = the size of difference in daily morphine equivalent dose we wish to detect, expressed in mg; and \(N_{0.80}\) = the sample size assuming a 20% dropout rate (27). A study in which per-treatment-arm group sizes were 50 or less was deemed feasible.

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