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Original Article

Flurbiprofen axetil reduces postoperative sufentanil consumption and enhances postoperative analgesic effects in patients with colorectal cancer surgery

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Abstract: To investigate the effects of different strategies of flurbiprofen axetil (FA) administration on postoperative pain and sufentanil (SF) consumption after open colorectal cancer (CRC) surgery. Forty patients undergoing elective CRC resection were divided into two groups (n = 20 each). Patients in the F_{50+50} group received 50 mg of intravenous FA 30 min before skin incision and six hours after the first dose; patients in the F_{100} group received 100 mg of intravenous FA 30 min before skin incision. Perioperative plasma FA (C_{FA}) and SF concentrations (C_{SF}) were determined. Analgesic and sedative efficacy were evaluated using the visual analogue scale (VAS), Bruggman Comfort Scale (BCS), and Ramsay sedation scale. The time to the first PCIA trigger, the number of patients that pressed the PCIA trigger within 24 h after surgery, and the cumulative doses of SF consumption within 6 and 24 h after surgery were recorded. At postoperative 6 and 24 h, C_{FA} was significantly higher, C_{SF} was significantly lower, and the number of patients that pressed the PCIA trigger and the consumption of SF were significantly lower in the F_{50+50} group compared with the F_{100} group. At postoperative 4 h, VAS and BCS were significantly lower in the F_{50+50} group compared with the F_{100} group ($P < 0.05$). An administration strategy that maintains a relatively high plasma FA concentration at 6-24 h post-operatively may reduce postoperative inflammatory pain and SF-requirement in patients undergoing CRC resection.

Keywords: Flurbiprofen axetil, pharmacokinetics, sufentanil consumption, cytokine, colorectal cancer

Introduction

Opioids are some of the most commonly used agents for perioperative analgesia during colorectal cancer (CRC) resection [1]. CRC resection represents a major perioperative stress, and is associated with a significant increase in postoperative levels of plasma inflammatory markers [2]. Increased levels of proinflammatory cytokines can induce sensitization of the peripheral and central nervous systems, and lead to hyperalgesia, postoperative inflammatory pain, and increased postoperative opioid-requirement [3]. However, opioids cause side-effects including respiratory depression and excessive sedation. In patients undergoing gastrointestinal surgery, important clinical effects of opioids include nausea, vomiting, constipation, and suppression of postoperative intestinal function. Therefore, efforts are directed at reducing postoperative opioid consumption in patients undergoing CRC resection. Alternative multimodal strategies involving non-steroidal anti-inflammatory drugs (NSAIDs) and opioids may be more applicable for perioperative analgesia in these patients.

The NSAID flurbiprofen axetil (FA) is an injectable nonselective cyclooxygenase (COX) inhibitor that is widely used for postoperative pain relief. FA exerts its analgesic effect by inhibiting prostaglandin synthesis. Patented FA technology uses emulsified lipid microspheres that have a high affinity for inflammatory tissues to achieve targeted drug therapy [4]. Currently, various modes for administering FA are applied in clinical settings, including 1 $mg \cdot kg^{-1}$ via intravenous injection (i.v.) [5, 6], 0.1 $mg \cdot kg^{-1} \cdot h^{-1}$ via

continuous venous infusion [7] and 50 mg [8] or 100 mg [9] via i.v. injection. In addition, FA is often used as preemptive analgesia by anesthesiologists [8], and is routinely applied in the adjuvant management of postoperative pain by surgeons [7].

The effect of administering perioperative FA analgesia on patient opioid consumption, for postoperative pain, is unknown. This randomized, double-blind clinical trial was designed to investigate the efficacy of a single bolus dose of preoperative FA versus two smaller preoperative and postoperative doses of FA on postoperative pain, sufentanil (SF) consumption, and cytokine release in patients undergoing CRC resection. Both protocols resulted in the same cumulative FA dose; however, the single bolus dose was expected to result in a decreasing perioperative plasma FA concentration, while the divided doses were expected to lead to a relatively steady-state plasma FA concentration. The objectives of this study were to investigate the effects of different protocols for perioperative administration of FA on (i) postoperative pain control and SF consumption and (ii) postoperative serum cytokine levels in patients undergoing CRC resection.

Materials and methods

Study subjects

Forty patients aged 37-69 years were included in this clinical trial. Inclusion criteria were 1) patients with an American Society of Anesthesiologists (ASA) Classification of Physical Status I/II; 2) scheduled for elective CRC surgery; 3) able to comprehend the concept of the Visual Analogue Scale (VAS) and Bruggman Comfort Scale (BCS); and 4) able to correctly use the patient-controlled intravenous analgesia (PCIA) trigger. Exclusion criteria were: 1) patients who had received NSAIDs, opioids, or other analgesics during the 24-h preoperative period; 2) patients with a history of allergic reaction to opioids and NSAIDs; 3) patients with any contraindications for the use of NSAIDs, such as coagulation disorders, gastrointestinal ulcer, and heart and renal disease; and 4) patients with preoperative hemoglobin < 100 $g{\cdot}L^{-1}$ and perioperative blood transfusion. All anesthesia and operative procedures were performed by the same group of anesthesiologists and surgeons. All patients were preoperatively evaluated with the Beck Depression Inventory (BDI) [10].

This clinical trial was approved by the Ethics Committee of the Second Affiliated Hospital, Harbin Medical University (Chinese Clinical Trial Registry ChiCTR-TRC-14004342). Informed consent was obtained from all patients prior to study enrollment.

Study treatment and procedures

Patients were randomly allocated to one of two groups: F_{100} or F_{50+50} (n = 20 patients each). Thirty minutes before skin incision, the patients in the F_{100} group were administered FA (Beijing Taide Pharmaceutical Co., Ltd.) 100 mg/10 mL i.v.; the patients in the F_{50+50} group were administered FA 50 mg/5 mL and 5 mL intralipid i.v. six hours after the first dose, patients in the F_{100} group were administered 5 mL intralipid i.v. as placebo; patients in the F_{50+50} group were administered FA 50 mg i.v.

During the operation, at the closure of the peritoneum, patients were connected to the PCIA and were allowed to self-administer SF 0.04 $\mu g{\cdot}kg^{-1}{\cdot}h^{-1}$ (SF 2 $mL{\cdot}h^{-1}$ continuous background infusion; 2 mL at each trigger pull; 2 mL of a loading dose; 15 min of lockout time).

Randomization was carried out using a computer program generating an odd and even number sequence. The trial was performed by three investigators in a double-blinded manner. The first investigator prepared each test solution in a syringe and was responsible for subject grouping and i.v. injection of the test solution. The second investigator, who was blinded to the type of test solution and subject grouping, performed anesthesia management, monitored vital signs, and collected blood samples at each timepoint. The third investigator, who was also blinded to all trial information, was responsible for recording and analyzing the perioperative scores and experimental data.

Standard monitoring was applied to all patients, including pulse oximetry, electrocardiography, capnography, and invasive arterial blood pressure. General anesthesia was induced with an i.v injection of midazolam (0.05 $mg{\cdot}kg^{-1}$), lidocaine (1.0-1.5 $mg{\cdot}kg^{-1}$), propofol (1.5-2.0 $mg{\cdot}kg^{-1}$), SF (0.3 $\mu g{\cdot}kg^{-1}$), and rocuronium (0.6 $mg{\cdot}kg^{-1}$) intravenously. Tracheal intubation was per-

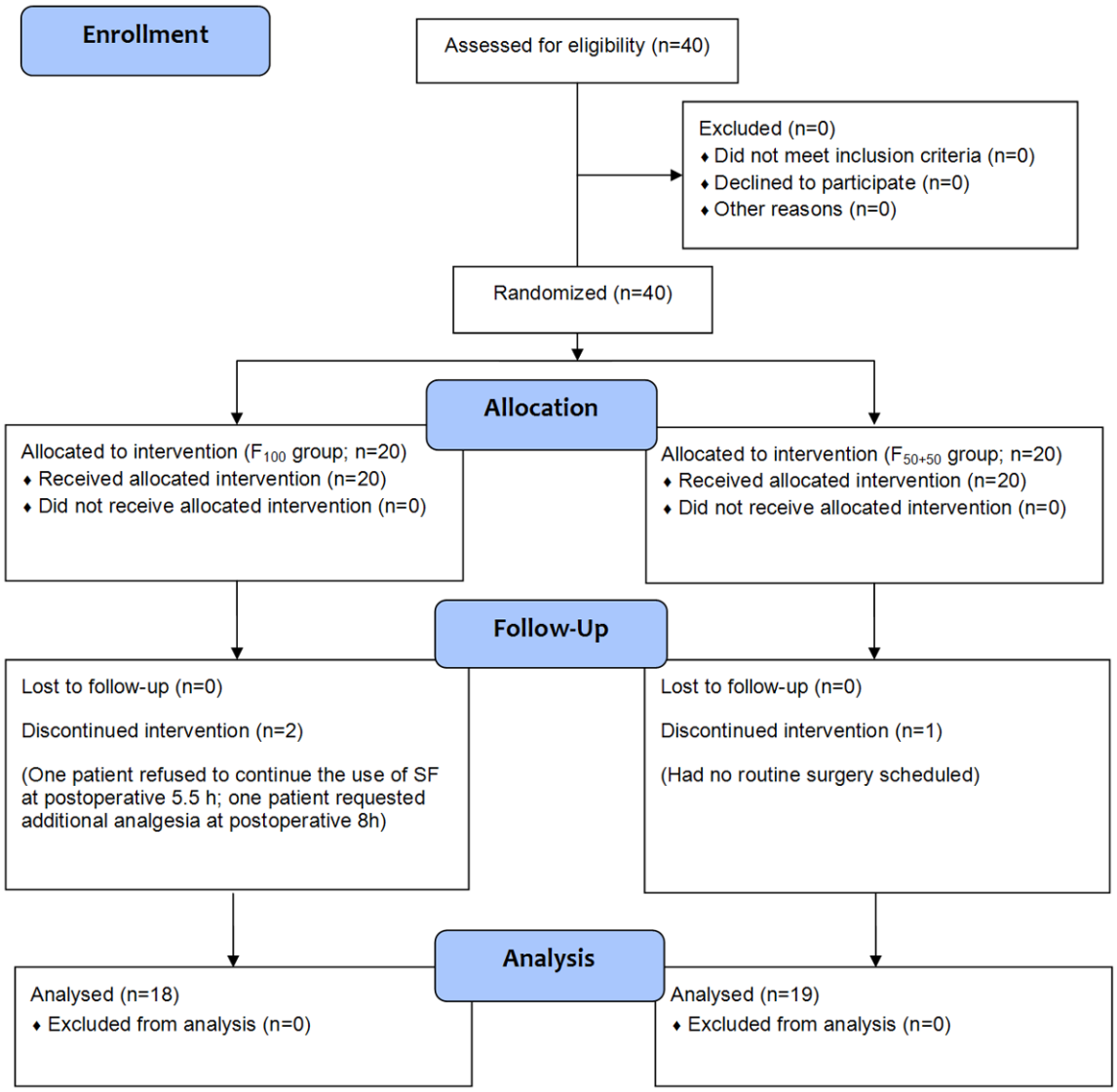

Figure 1. Study design.

formed. Tidal volume of mechanical ventilation was 10 ml·kg^{-1}; respiratory rate was adjusted to maintain the partial pressure of end-tidal carbon dioxide ($P_{ET}CO_2$) between 35-45 mmHg. General anesthesia was maintained with continuous infusion of remifentanil (8-10 μg·kg^{-1}·h^{-1}, i.v.) and inhalation of sevoflurane in oxygen (0.7-0.9 MAC), which were adjusted to maintain steady hemodynamic indices. All patients received lactated ringer's solution and hydroxyethyl (6-8 mL·kg^{-1}·h^{-1}) perioperatively (colloidal: crystal = 2:1). When blood pressure was < 90 mmHg, i.v. fluid infusion was increased or ephedrine (6-10 mg, i.v.) was administered. All patients were taken to the postoperative anesthesia care unit after surgery.

Outcome measures

This trial had seven time points: T_0, preoperation; T_1, 15 min after the first dose of FA; T_2, end of surgery; T_3, postoperative 2 h; T_4, 6 h after the first dose of FA; T_5, postoperative 4 h; T_6, postoperative 6 h; T_7, postoperative 24 h.

The primary outcome measures were plasma FA concentrations (C_{FA}) at T_1-T_7 (except for T_3 and T_5) and plasma SF concentrations (C_{SF}) at postoperative T_2, T_6, and T_7. C_{FA} and C_{SF} were detected using high-performance liquid chromatography (HPLC; Shimadzu LC20A, Japan) with flurbiprofen (FP 1408-013A2; Mississauga, Canada) and sufentanil citrate (171259-

Table 1. Patient demographics and clinical data

	F_{100} (n = 18)	F_{50+50} (n = 19)	*P*
Age (yr)	59.06±9.40	54.37±8.59	0.122
Body weight (kg)	66.36±10.63	61.68±10.54	0.188
Gender (F/M)	11/7	14/5	0.414
BDI score	6.11±1.94	6.79±1.99	0.301
Operation time (min)	154.44±28.02	147.63±30.16	0.482
Incision length (cm)	18.67±1.41	18.84±2.17	0.774
Type of surgery (n)			0.641
Hemicolectomy (left)	3	5	
Hemicolectomy (right)	5	3	
Sigmoid colectomy	3	4	
Miles	6	4	
Dixon	1	3	
Blood loss (mL)	202.78±55.50	192.11±58.36	0.573
Fluid administration (mL)	1575.00±337.92	1478.95±379.44	0.423
Remifentanil (mg)	1.71±0.20	1.76±0.28	0.505

BDI, Beck Depression Inventory; M, Male; F, Female. Values are mean ± SD except for gender and type of surgery.

200601; NICPBP) as the standards for quantitative analyses.

Postoperative pain intensity was assessed using a 10-cm VAS [11] (with endpoints labeled "no pain" and "worst possible pain") and the BCS [12] (scores ranging between 0 "persistent pain" and 4 "cough is painless"). The patients' levels of sedation were evaluated using the Ramsay scale (scores ranging between 1 "anxious and agitated" to 6 "non-responsive") [13]. Observation indices also included the time to the first PCIA trigger, the number of patients that pressed the PCIA trigger within 24 h after surgery, and total SF consumption within 6 and 24 h after surgery. The patients were permitted to press the PCIA trigger when their VAS score was > 4. Additional analgesia was given if patients could not maintain their VAS score < 6; these patients were excluded from the analyses. Adverse effects, such as drowsiness, dizziness, nausea, vomiting, and fever, were recorded during the 24-h postoperative period.

The secondary outcome measures were plasma concentrations of IL-6 and IL-10 at T_0, T_6, and T_7. Blood (3 mL) sampled at T_0-T_7 (except for T_3 and T_5) was collected into EDTA tubes and immediately centrifuged at 3000 rpm for 15 minutes at 4°C. Subsequently, plasma was stored at -80°C until future use. Plasma concentrations of IL-6 and IL-10 at T_0, T_6, and T_7 were measured with commercially available quantitative sandwich enzyme-linked immunosorbent assay kits (BOSTER, China) according to the manufacturers' instructions. The sensitivities of the assays for IL-6 and IL-10 were 0.3 and 0.5 pg·mL^{-1}, respectively.

Statistical analysis

The sample size was based on a preliminary trial conducted by the authors. With an alpha level of 0.05 and a beta level of 0.1 (mean: 80.84 μg in the F_{100} group and 66.15 μg in the F_{50+50} group; SD 13.13 μg within 24 h after surgery; one-sided hypothesis), a minimum sample size of 15 patients per group were required to detect a difference in SF consumption. Twenty patients were recruited to each group to account for possible dropouts and protocol breaches.

All statistical analyses were performed using SPSS software (version 13.01S; Beijing Stats Data Mining Co. Ltd., Beijing, China). Normality of the distribution was assessed with the Kolmogorov-Smirnov test. Parametric data are described as means and standard deviations and non-parametric data are described as medians and interquartile ranges. Gender and the type of operation were analysed using the Pearson Chi-squared test. Between-group comparisons of the incidence of adverse events were evaluated by the Fisher's exact test. VAS, BCS, and Ramsay scores were compared using the Mann-Whitney rank sum test. Plasma levels of IL-6, and IL-10 were compared using repeated-measures analysis of variance (ANOVA). For other variables with a normal distribution, an independent two-sample t-test was used for intergroup comparison. *P*-values < 0.05 were considered statistically significant.

Results

Forty patients were randomly assigned to either the F_{100} or F_{50+50} group (n = 20 each). In the F_{100} group, two patients discontinued the intervention. Of these, one patient refused to continue the use of SF at postoperative 5.5 h, and one patient requested additional analgesia at post-

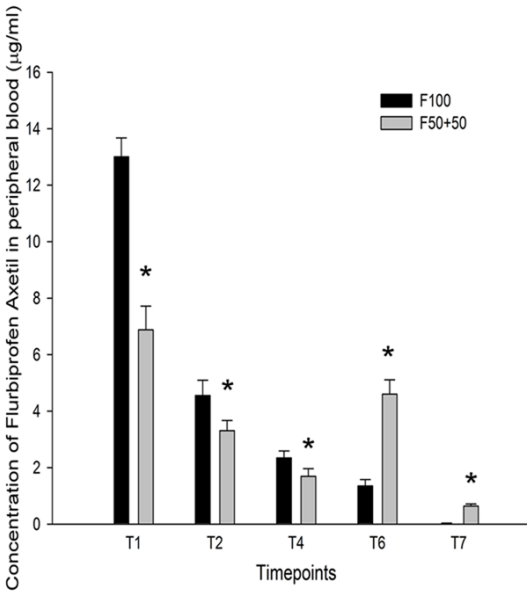

Figure 2. Concentration of flurbiprofen axetil (FA) in plasma. Values are mean ± SD. *$P < 0.05$, compared with F_{100} group. Time points: T_1, 15 min after the first dose of FA; T_2, end of surgery; T_4, 6 h after the first dose of FA; T_6, postoperative 6 h; T_7, postoperative 24 h.

operative 8 h. In the F_{50+50} group, one patient had no scheduled surgery. Thirty-seven patients were included in the analyses, 18 in the F_{100} group and 19 in the F_{50+50} group (**Figure 1**).

Patient demographic and clinical characteristics

There were no significant differences in patient age, body weight, gender, BDI score, duration of surgery, incision length, type of surgery, blood loss, fluid administration, or intraoperative remifentanil consumption between the F_{100} and F_{50+50} groups (**Table 1**).

Primary outcome measures

At T_6 and T_7, C_{FA} was significantly higher in the F_{50+50} group compared with the F_{100} group (**Figure 2**; $P < 0.05$), and C_{SF} was significantly lower in the F_{50+50} group compared with the F_{100} group (**Figure 3**; $P < 0.05$).

The time to the first PCIA trigger was not statistically different between the F_{50+50} and F_{100} groups. The number of patients that pressed the PCIA trigger and the consumption of SF 6 and 24 h postoperatively were significantly lower in the F_{50+50} group compared with the F_{100} group (**Table 2**; $P < 0.05$).

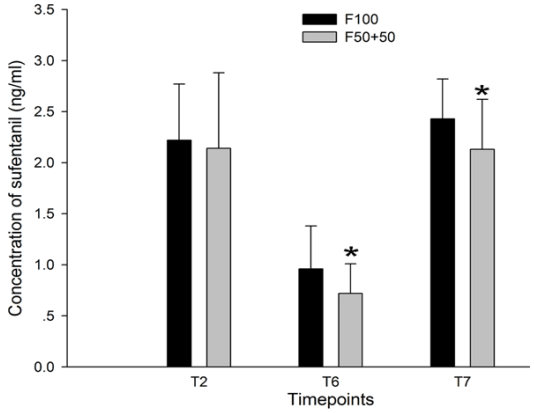

Figure 3. Concentration of sufentanil (SF) in plasma. Values are mean ± SD. *$P < 0.05$, compared with F_{100} group. Time points: T_2, end of surgery; T_6, postoperative 6 h; T_7, postoperative 24 h.

VAS and BCS scores were significantly lower at T_5 in the F_{50+50} group compared with the F_{100} group (**Figure 4**; $P < 0.05$). There were no significant differences in Ramsay scores at that time. There were no significant differences in VAS, BCS, and Ramsay scores at T_2, T_3, T_6, and T_7.

There were no significant differences in the incidence of postoperative adverse events between the two groups (**Table 3**).

Secondary outcome measures

There were significant differences in pre- and postoperative IL-6 and IL-10 levels, and the ratio of IL-6 to IL-10 between groups (**Figure 5**). IL-6 and IL-10 levels increased from preoperation to the end of surgery, and peaked at postoperative 6 h in both groups. At T_6, the ratio of IL-6 to IL-10 was significantly different between the F_{50+50} and F_{100} groups ($P < 0.05$). IL-6 levels were slightly lower and IL-10 levels were slightly higher in the F_{50+50} group compared with the F_{100} group; however, these differences were not statistically significant.

Discussion

This study indicates that the pharmacokinetics and pharmacodynamics of perioperative FA may be used as a clinical guide for the administration of postoperative analgesia. Two strategies for the administration of FA were used; both achieved the same cumulative dose. The F_{50+50} strategy involved the perioperative

Table 2. Sufentanil consumption

	F_{100} (n = 18)	F_{50+50} (n = 19)	*P*
Time to first PCIA trigger (min)	52.50±7.67	51.58±6.67	0.699
Consumption of SF during 6 h (μg)	24.60±6.31	19.49±6.88	0.024
Consumption of SF during 24 h (μg)	79.32±12.72	66.93±11.12	0.003
Number of patient's that pressed PCIA trigger (n)	6.67±2.40	4.95±2.09	0.026

SF, Sufentanil; Values are mean ± SD.

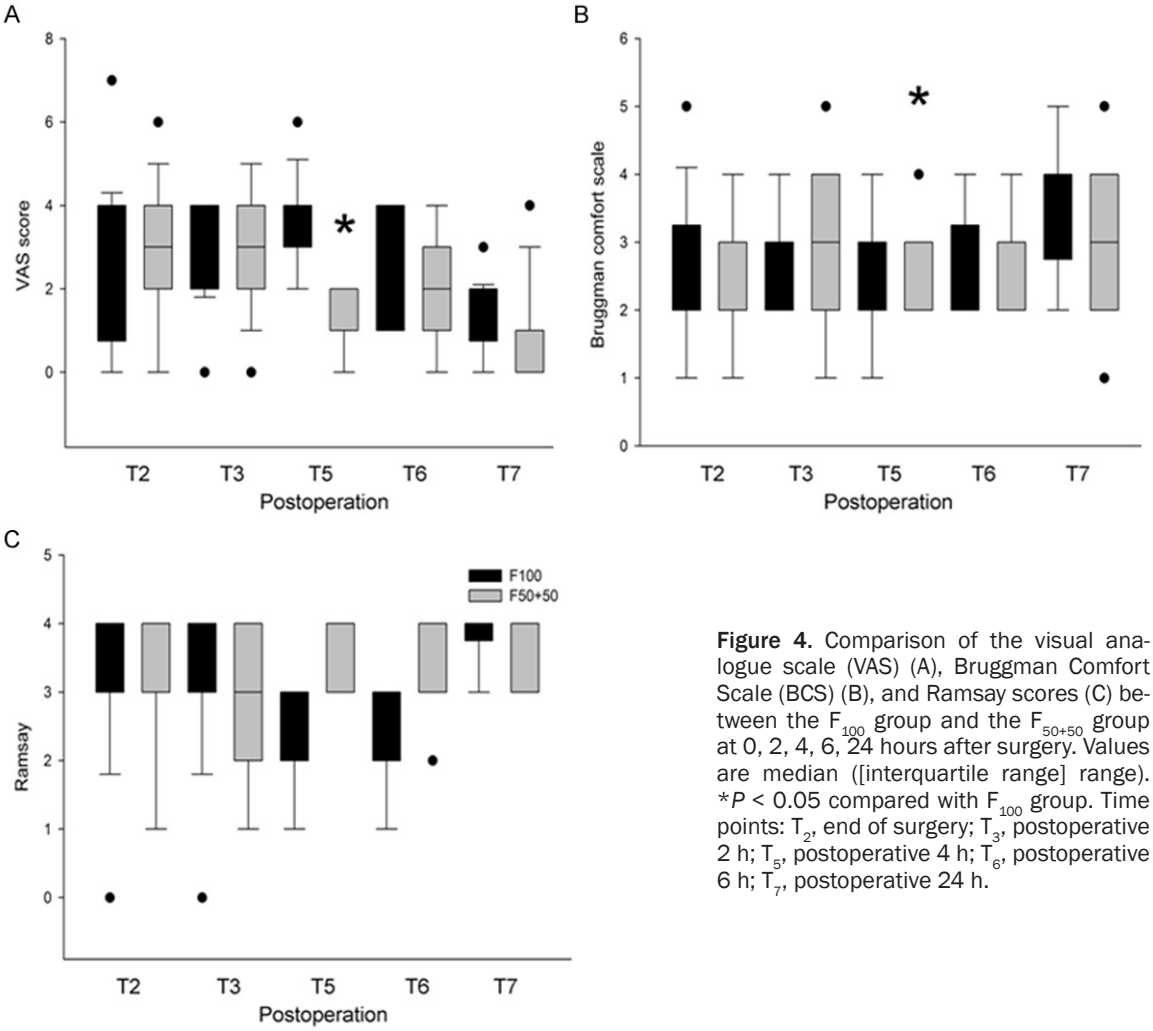

Figure 4. Comparison of the visual analogue scale (VAS) (A), Bruggman Comfort Scale (BCS) (B), and Ramsay scores (C) between the F_{100} group and the F_{50+50} group at 0, 2, 4, 6, 24 hours after surgery. Values are median ([interquartile range] range). $*P < 0.05$ compared with F_{100} group. Time points: T_2, end of surgery; T_3, postoperative 2 h; T_5, postoperative 4 h; T_6, postoperative 6 h; T_7, postoperative 24 h.

Table 3. Incidence of adverse events

	F_{100} (n = 18)	F_{50+50} (n = 19)	*P*
Nausea and vomiting	0	1	1.000
Slow to respiratory response	2	1	0.604
Fever	0	1	1.000

administration of two low doses of FA within a short period of time. This maintained a relatively steady-state plasma concentration of FA throughout the study period, which may have prolonged the pharmacological effect of FA. Indeed, this strategy resulted in significantly decreased VAS and BCS scores and opioid consumption during the early postoperative period. Furthermore, the ratio of IL-6 to IL-10 was down-regulated 6 h after surgery.

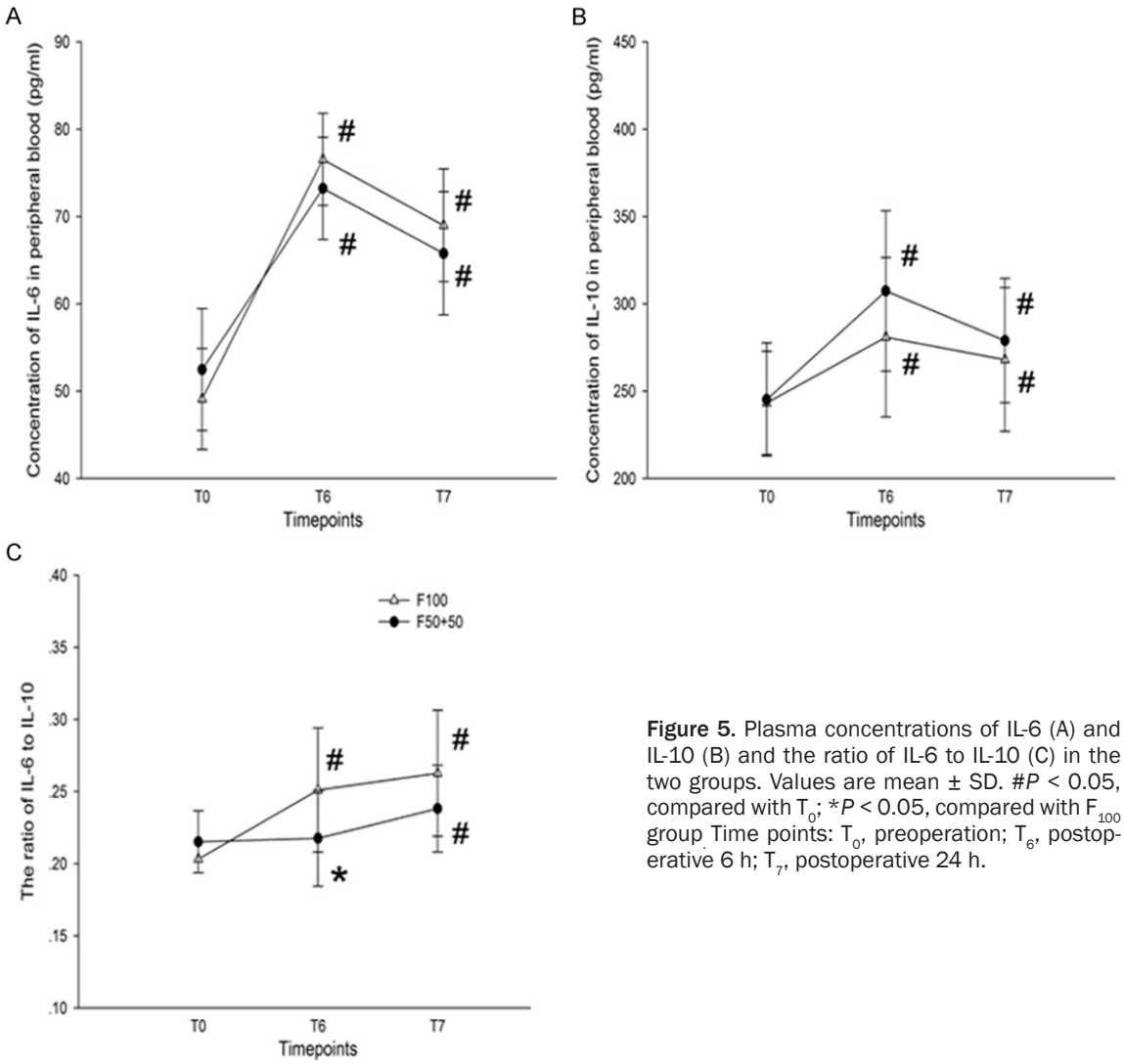

Figure 5. Plasma concentrations of IL-6 (A) and IL-10 (B) and the ratio of IL-6 to IL-10 (C) in the two groups. Values are mean ± SD. #$P < 0.05$, compared with T_0; *$P < 0.05$, compared with F_{100} group Time points: T_0, preoperation; T_6, postoperative 6 h; T_7, postoperative 24 h.

Evidence suggests that perioperative FA may reduce postoperative pain, inhibit the release of inflammatory factors, and improve intestinal function in patients undergoing CRC surgery [6]. Intravenous FA injection is composed of emulsified lipid microspheres, which provide a novel targeted drug delivery system to inflammatory tissues. The lipid microsphere technique enables efficient delivery and accumulation of FP, the active metabolite of FA, at sites of damaged tissue and inflammation. FA is hydrolyzed to FP by a plasma carboxylic esterase. Studies in rat and monkey animal models and healthy volunteers report that FP is present in the blood within 5 min of FA administration and peaks within 6-7 min of FA administration; the response is dose-dependent between FA 10-80 mg. The analgesic effect of FA is apparent within 30 min of FA administration, and the elimination half-life is 5.8 h. The elimination half-life of the lipid microspheres is approximately 12 min; therefore, they rapidly disappear from the blood. After 24 h of administration, approximately 50% of FP metabolites are discharged in the urine [4, 14-18].

In the current study, we used i.v. doses of FA of 100 mg and 50 mg because there are no data in the literature to support dosing according to body weight. The results showed significant differences in plasma FA concentrations between the groups intraoperatively, probably because the FA doses at first administration were so different. However, the plasma concentration of FA in the F_{100} patients was not double that of the F_{50+50} patients at T_2 or T_4. This observation

may explain, in part, the analgesic ceiling effect of NSAIDs [19]. There were no significant differences in plasma SF concentration; intraoperative remifentanil consumption; or VAS, BCS, and Ramsay scores among all patients in the immediate post-operative period. We propose that sevoflurane may have had an intraoperative analgesic effect, and that intraoperative application of a combination of various sedative and analgesic agents caused the comparable analgesic effects of FA 100 mg and 50 mg during the operation and immediately afterwards. A second dose of FA was administered to F_{50+50} patients at T_3 (6 h after the first i.v. administration and approximately postoperative 3 h) in an attempt to maintain a relatively steady-state plasma concentration of FA throughout the study period in these patients. At this time, the same cumulative dose of FA was achieved in both groups, and pain scores, SF consumption, and expression of inflammatory cytokines within the 3-24 h postoperative period were the primary outcomes measured. At postoperative 4 h, both VAS and BCS scores were significantly lower in the F_{50+50} group compared to the F_{100} group. Probably because the relatively higher FA plasma concentration in the F_{50+50} group provided a critical moment of FA/SF multimodal analgesia that was not experienced by the F_{100} group. Surprisingly, the VAS, BCS, and Ramsay scores at T_6 and T_7 were significantly lower in patients with a lower plasma FA concentration. This could be explained by the significantly higher plasma SF concentration in these patients, which may have compensated for the lower plasma FA concentration. As such, both groups of patients could have achieved the same level of postoperative pain through multimodal analgesia with different concentrations of FA and SF. Accordingly, SF consumption and the number of patients that pressed the PCIA trigger was significantly greater in the patients that had a lower plasma FA concentration.

The goal of perioperative analgesic management of CRC surgical patients is minimizing nociception and proinflammatory responses [1]. Tissue injury produced by multi-technique operations is associated with nociception and a marked increase in postoperative cytokine release [20]. The feedback cascade between nociception and proinflammatory markers generates a significant increase in proinflammatory cytokines such as IL-6 [21]. Among the human body responses-caused by surgery, the serum level of IL-6 is a sensitive index of the degree of surgical stress [22-24]. IL-6 can lead to hyperalgesia through sensitization of the peripheral and central nervous systems [3]. IL-6 may indirectly regulate pain via cytokine-induced release of other neuroactive substances, such as nitric oxide, oxygen free radicals, prostaglandins, and excitatory amino acids [25]. At the same time, IL-10 levels increase during major surgery. IL-10 tends to maintain homeostasis as it has strong anti-inflammatory activities through the inhibition of prostaglandin production [26]. Previous studies show that NSAID administration after major surgery is associated with increased IL-10 production [27, 28], and there may be a negative feedback between prostaglandin synthesis and the production of IL-10. Prostaglandins had a vital role in the induction of IL-10 in human monocytes; in turn, IL-10 inhibits prostaglandin production [29]. Based on these observations, we propose that the relatively steady-state plasma concentration of FA and/or SF sparing in the current study regulated the IL-6: IL-10 ratio, favoring the production of the anti-inflammatory IL-10 over the pro-inflammatory IL-6. This may have directly or indirectly regulated postoperative cytokine release, reduced injury-induced inflammatory pain, decreased SF-requirement, and enhanced postoperative analgesic effects.

There are several limitations to the current study. First, patients were not stratified according to preoperative neoplasm staging, which may impact the accuracy of the results. Evidence suggests that levels of inflammatory mediators vary in association with tumor stage [30]. Second, causative data to indicate that SF directly reduced the immunomodulatory effect of cytokines are not reported; this area of research warrants further investigation. Third, plasma creatinine levels may be useful for the assessment of adverse events; however, these data are not available for this study. Fourth, the study was terminated at postoperative 24 h; however, cytokine release may persist 24-36 h after surgery [31]. Finally, we did not document the recovery of intestinal function after surgery, although i.v. FA may accelerate bowel function, including the time to first flatus and bowel movements [6]. Future research should be directed at determining whether the maintenance of steady-state plasma FA concentra-

tions in patients undergoing CRC resection affects postoperative intestinal function.

In conclusion, perioperative administration of two low doses of FA within a short period of time appears to maintain a relatively higher plasma FA concentration at 6-24 h post-operatively in patients undergoing CRC resection. This may reduce postoperative opioid consumption and enhance analgesic effects after surgery in these patients. Considering the pharmacodynamics and pharmacokinetics of FA may be useful for guiding perioperative FA administration during the management of patients undergoing CRC resection.

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Disclosure of conflict of interest

None.

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