Comparison of postoperative analgesia between dezocine plus flurbiprofen axetil and sufentanil in patients with CRC undergoing tumor resection: A prospective, observational study

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Abstract. Flurbiprofen axetil is a nonsteroidal anti-inflammatory drug used for analgesia. Its combination with dezocine has previously shown a superior postoperative analgesic effect compared with that of opioids. The present study compared the analgesic effect between dezocine plus flurbiprofen axetil (DFA) and sufentanil in patients with colorectal cancer (CRC) following resection of the tumor. The study was performed as a prospective, observational study. It included 107 patients who were treated using a patient-controlled analgesia (PCA) pump following the resection of CRC. Patients in the DFA group were given a loading dose of 5 mg dezocine and 50 mg flurbiprofen axetil, followed by PCA with a combination comprising 30 mg dezocine, 200 mg flurbiprofen axetil and 8 mg ondansetron. Patients in the control group were treated with sufentanil at a loading dose of 5-10 μg followed by PCA with a combination of 100 μg sufentanil and 8 mg ondansetron. The DFA group reported lower pain numerical rating scale scores at 2 h (2.4±1.2 vs. 2.9±1.2) and 12 h (2.0±1.0 vs. 2.5±1.2) and reduced rates of moderate-to-severe pain at 12 h (6.7 vs. 21.0%) compared with those in the control group. In addition, the number of PCA boluses in the DFA group was lower than that in the control group [median (interquartile range), 6.0 (4.5-8.5) vs. 8.5 (5.0-11.0)]. The total satisfaction rate was increased, albeit not significantly, in the DFA group compared with that in the control group (80.0 vs. 62.9%). The levels of tumor necrosis factor-α at 24 and 48 h, and of interleukin-6 at 24 h were decreased in the DFA group compared with those in the control group. The incidences of adverse events did not differ between the groups. These findings indicate that DFA provides more effective analgesia, improves patient satisfaction and reduces the levels of pro-inflammatory cytokines with similar adverse effects compared with those of sufentanil in patients after CRC resection.

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Introduction

Colorectal cancer (CRC) was the third most commonly occurring cancer and the second leading cause of cancer-associated deaths worldwide in 2022 (1). For patients with locoregional CRC, surgical resection is the primary treatment with curative potential (2). However, most patients undergoing the resection of CRC experience postoperative pain and require postoperative analgesic management (3,4). Opioids, such as morphine and sufentanil, are the main agents used for postoperative analgesia in patients with CRC undergoing tumor resection (5-8). However, the use of opioids potentially induces adverse events, including hyperalgesia and physical dependence, which can lead to opioid use disorder and reduced patient satisfaction (9-11).

Dezocine is an amino-tetrahydronaphthalene derivative widely used in China as an analgesic, which produces a pain-relieving effect through the partial activation of μ and κ receptors as well as the inhibition of norepinephrine reuptake (12,13). The specific pharmacological mechanisms of dezocine provide a similar analgesic effect to those provided by typical opioids, including morphine and sufentanil, but with fewer adverse effects, such as respiratory depression, immunosuppression, and the disruption of intestinal motility (14-17). In addition to being used as a monotherapy, dezocine is commonly combined with nonsteroidal anti-inflammatory drugs in clinical settings, and studies suggest that such combinations allow a reduced dosage of dezocine to achieve enhanced analgesic effects (18-20). Therefore, the combination of dezocine and nonsteroidal anti-inflammatory drugs appears to be a promising analgesic regimen for patients undergoing surgery.

Flurbiprofen axetil is a prodrug of flurbiprofen with a high affinity for inflammatory tissues and is one of the most commonly used nonsteroidal anti-inflammatory drugs for analgesia in China (12,21,22). It relieves pain by inhibiting the production of prostaglandin; it also reduces pro-inflammatory cytokines, such as tumor necrosis factor-α (TNF-α) and interleukin 6 (IL-6), which further alleviates inflammatory pain (23,24). Given the promising analgesic effects and distinct analgesic mechanisms of flurbiprofen axetil and dezocine,

their combination may be a promising regimen for postoperative pain management (25,26). Recently, several studies have suggested that the postoperative analgesic effect of dezocine plus flurbiprofen axetil (DFA) is greater than that of opioids for patients undergoing surgery (25-27). For instance, one study found that postoperative pain was reduced in patients who had undergone abdominal surgery when treated with DFA compared with opioids (26). In another study, postoperative pain and the level of TNF-α in patients with resectable non-small cell lung cancer were reduced by a greater extent by DFA than by dezocine (25). Therefore, it is speculated that DFA may provide analgesia superior to that of opioids in patients with CRC undergoing tumor resection. However, this hypothesis remains unverified.

Therefore, the current prospective, observational study aimed to compare the postoperative analgesic effect, levels of pro-inflammatory cytokines, patient satisfaction and safety profiles between DFA and sufentanil in patients with CRC following tumor resection.

Materials and methods

Patients. Between February 2020 and September 2023, the current prospective observational study included 107 patients with CRC who received postoperative patient-controlled anesthesia (PCA) with DFA or sufentanil. The patients were enrolled at the Fifth Affiliated Hospital of Wenzhou Medical University (also known as Lishui Hospital of Zhejiang University; Lishui, China). The inclusion criteria comprised the following: i) Confirmed as having CRC; ii) >18 years old; iii) American Society of Anesthesiologists (ASA) physical status I or II; iv) underwent tumor resection surgery; v) received postoperative analgesia with a DFA or sufentanil PCA pump; vi) had normal cognitive function and were able to complete all required assessment scales; and vii) were willing to provide blood samples for the detection of pro-inflammatory cytokines. The exclusion criteria comprised: i) Known allergies to the study drugs; ii) distant metastases; iii) severe hepatic, renal or cardiorespiratory abnormalities; iv) history of abdominal surgery or other malignant diseases; v) history of psychoactive drug dependence; and vi) women who were pregnant or lactating. The study was approved by the Ethics Committee of Lishui Hospital of Zhejiang University (approval no., 2017056). All patients provided written informed consent.

Postoperative analgesia. This was a prospective, observational and non-interventional study, so the patients' treatment was not intervened with. The anesthetists decided the medication based on their experience, patient's comorbidities, patient's age and patient's weight. According to the medications received, patients who received DFA via PCA pump were considered as the DFA group, while patients who received a sufentanil via a PCA pump were considered as the control group. The patients in the DFA group were given an intravenous infusion of 5 mg dezocine and 50 mg flurbiprofen axetil as loading dose, followed by the continuous administration via PCA pump of a composition containing 30 mg dezocine, 200 mg flurbiprofen axetil and 8 mg ondansetron. All medications were diluted to 100 ml with saline. The PCA pump was set up to provide automatic infusion at a background dose of 2 ml/h, and patients were able to self-administer additional single 1-ml doses as required, with a 15-min lock time after each additional dose to prevent overdose. Patients in the control group were given 5-10 μg sufentanil as an intravenous infusion loading dose, followed by a PCA pump containing 100 μg sufentanil and 8 mg ondansetron, also diluted in saline to 100 ml. The PCA pump settings in the control group were the same as those in the DFA group. For some patients, the dosage was adjusted according to their body weight to meet the demands of personalized treatment.

Assessment. Clinical characteristics were collected for study analysis, including age, sex, weight, ASA grade, tumor location, and T (tumor size and extent), N (nearby lymph node involvement) and tumor-node-metastasis (TNM) stages (28,29). The operation time and intraoperative blood loss were also documented. The pain was evaluated on a numerical rating scale (NRS) at 2, 6, 12, 24 and 48 h after surgery. The pain score on the NRS scale ranged from 0-10 as follows: 0, no pain; 1-3, mild pain; 4-6 moderate pain; and 7-10, severe pain. Moderate-to-severe pain was defined as a pain NRS score of 4-10. The number of PCA boluses was also recorded. A patient satisfaction score was also collected, ranging from 1-5, with a higher rating indicating greater satisfaction as follows: 1, very dissatisfied; 2, dissatisfied; 3, neutral; 4, satisfied; and 5, very satisfied. Total satisfaction was defined as satisfied or very satisfied. In addition, patient's blood was collected 24 and 48 h after surgery and the serum TNF-α and IL-6 levels were detected using enzyme-linked immunosorbent assay kits (TNF-α, cat. no. PT518; IL-6, cat. no. PI330) from Beyotime Institute of Biotechnology. In addition, any adverse events were recorded for safety assessment.

Statistical analysis. Statistics were conducted using SPSS v.26.0 (IBM Corp.). Data are presented as the mean ± standard deviation, median (interquartile range) or n (%) as appropriate. Comparisons between the DFA and control groups were analyzed using unpaired Student's t-test, Wilcoxon's rank-sum test, χ^2 test or Fisher's exact test. $P<0.05$ was considered to indicate a statistically significant result.

Results

Comparison of baseline characteristics between the DFA and control groups. The DFA group included 45 patients, with a mean age of 55.1±11.6 years. There were 11 (24.4%) female and 34 (75.6%) male patients. Regarding the TNM stage, 6 (13.3%) patients were at stage I, 16 (35.6%) patients were at stage II and 23 (51.1%) patients were at stage III. The control group comprised 62 patients with a mean age of 57.9±10.7 years, among whom 21 (33.9%) patients were female and 41 (66.1%) were male. Regarding the TNM stage, 10 (16.1%) patients were at TNM stage I, 24 (38.7%) patients were at stage II, and 28 (45.2%) patients were at stage III. The age, sex, weight, ASA grade, tumor location, and T, N and TNM stages were not significantly different between the DFA and control groups (all $P>0.05$). The detailed baseline characteristics of the patients are listed in Table I.

Table I. Clinical characteristics.

Items	Control group (n=62)	DFA group (n=45)	P-value
Age (years)	57.9±10.7	55.1±11.6	0.206
Sex			0.293
Female	21 (33.9)	11 (24.4)	
Male	41 (66.1)	34 (75.6)	
Weight, kg	61.7±8.9	63.1±9.4	0.443
ASA grade			0.510
I	17 (27.4)	15 (33.3)	
II	45 (72.6)	30 (66.7)	
Tumor location			0.315
Rectum	19 (30.6)	18 (40.0)	
Colon	43 (69.4)	27 (60.0)	
T stage			0.592
T1	4 (6.5)	0 (0.0)	
T2	12 (19.4)	10 (22.2)	
T3	42 (67.7)	32 (71.1)	
T4	4 (6.5)	3 (6.7)	
N stage			0.248
N0	34 (54.8)	22 (48.9)	
N1	23 (37.1)	13 (28.9)	
N2	5 (8.1)	10 (22.2)	
TNM stage			0.530
I	10 (16.1)	6 (13.3)	
II	24 (38.7)	16 (35.6)	
III	28 (45.2)	23 (51.1)	

Data are shown as the mean ± standard deviation or n (%). DFA, dezocine plus flurbiprofen axetil; ASA, American Society of Anesthesiologists; TNM, tumor-node-metastasis.

In terms of surgical information, no difference was observed in operation time (P=0.211; Fig. 1A) or intraoperative blood loss (P=0.310; Fig. 1B) between the DFA and control groups.

Comparison of pain and PCA boluses between the DFA and control groups. Pain NRS scores at 2 h (P=0.030) and 12 h (P=0.026) were significantly decreased in the DFA group compared with those in the control group. However, the scores at 6, 24 and 48 h did not differ between the two groups (all P>0.05; Fig. 2A). The proportion of patients with moderate-to-severe pain at 12 h was significantly reduced in the DFA group compared with that in the control group (6.7 vs. 21.0%, respectively; P=0.041); whereas the rates at 2, 6, 24 and 4 8 h did not differ between the two groups (all P>0.05; Fig. 2B).

The number of PCA boluses administered was significantly lower in the DFA group compared with that in the control group (P=0.011; Fig. 3). These findings suggest that pain was relieved more effectively in the DFA group than in the control group.

Table II. Adverse events.

Items	Incidence, n (%)		P-value
	Control group (n=62)	DFA group (n=45)	
Nausea	9 (14.5)	4 (8.9)	0.379
Pruritus	5 (8.1)	3 (6.7)	1.000
Vomiting	4 (6.5)	2 (4.4)	1.000
Dizziness	3 (4.8)	2 (4.4)	1.000
Drowsiness	5 (8.1)	1 (2.2)	0.397
Constipation	2 (3.2)	0 (0.0)	0.508
Respiratory depression	1 (1.6)	0 (0.0)	1.000
Hypotension	1 (1.6)	0 (0.0)	1.000

DFA, dezocine plus flurbiprofen axetil.

Comparison of patient satisfaction between the DFA and control groups. Patient satisfaction varied between the DFA and control groups (P=0.031; Fig. 4A). The percentage of patients reporting total satisfaction in the DFA group was increased compared with that in the control group, but the difference between the groups did not achieve statistical significance (80.0 vs. 62.9%, respectively; P=0.057; Fig. 4B). These findings indicate that patient satisfaction was improved to some extent in the DFA group compared with that in the control group.

Comparison of pro-inflammatory cytokines between the DFA and control groups. The DFA group had decreased levels of TNF-α at 24 h (P=0.011) and 48 h (P=0.048) compared with those in the control group (Fig. 5A). In addition, the level of IL-6 at 24 h in the DFA group was lower than that in the control group (P=0.029), but its level at 48 h did not vary between the two groups (P=0.090) (Fig. 5B). These results indicate that pro-inflammatory cytokines were generally lower in the DFA group than in the control group.

Comparison of adverse events between the DFA and control groups. Adverse events in the DFA group included nausea (8.9%), pruritus (6.7%), vomiting (4.4%), dizziness (4.4%) and drowsiness (2.2%). In the control group, adverse events included nausea (14.5%), pruritus (8.1%), drowsiness (8.1%), vomiting (6.5%), dizziness (4.8%), constipation (3.2%), respiratory depression (1.6%) and hypotension (1.6%). The incidences of adverse events did not differ between the two groups (all P>0.05; Table II). These findings indicate that the safety of DFA was acceptable.

Discussion

Given the negative effects of postoperative pain on the physical function, recovery from surgery, quality of life and psychological status of patients, effective analgesic management is crucial for improving patient outcomes (30). In previous studies, flurbiprofen axetil combined with opioids

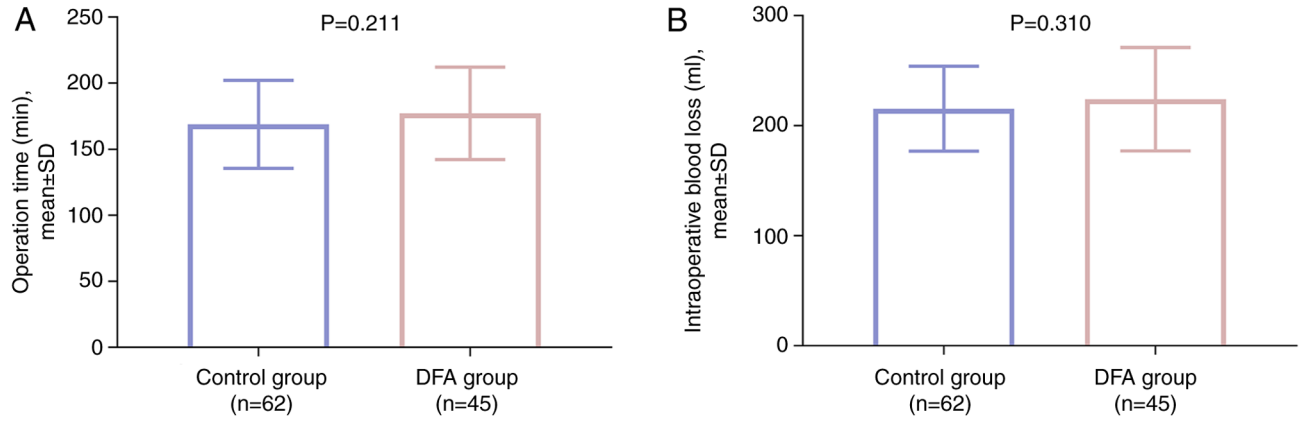

Figure 1. Operation time and intraoperative blood loss do not differ between the DFA and control groups. Comparison of (A) operation time and (B) intraoperative blood loss between the DFA and control groups. DFA, dezocine plus flurbiprofen axetil.

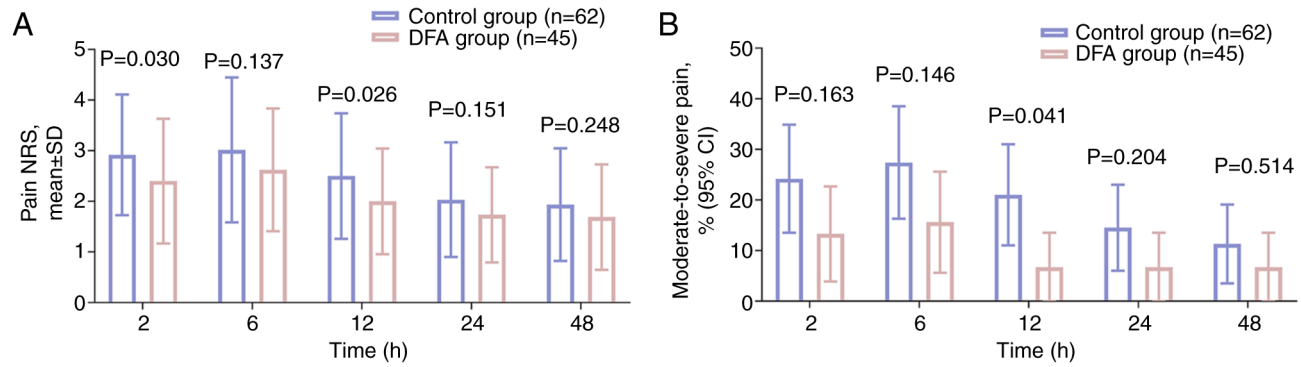

Figure 2. DFA treatment reduces the pain NRS score at 2 and 12 h and the proportion of patients with moderate-to-severe pain at 12 h compared with that in the control group. Comparison of (A) pain NRS scores and (B) moderate-to-severe pain rates at 2, 6, 12, 24 and 48 h in the DFA and control groups. NRS, numerical rating scale; DFA, dezocine plus flurbiprofen axetil.

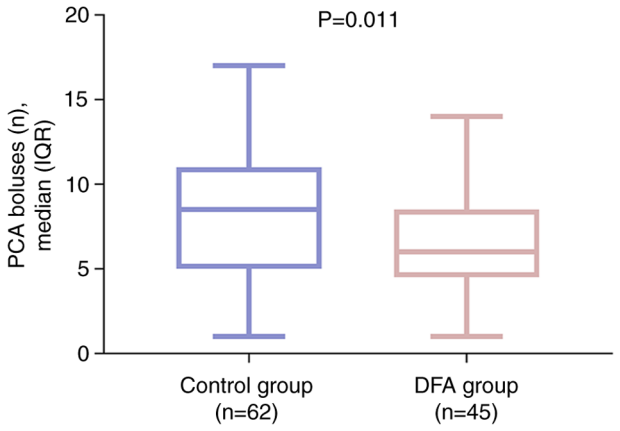

Figure 3. Number of PCA boluses in the DFA group is lower than that in the control group. PCA, patient-controlled anesthesia; DFA, dezocine plus flurbiprofen axetil; IQR, interquartile range.

was indicated to be more effective than opioid alone for the alleviation of postoperative pain in patients undergoing tumor resection (25,31). Similarly, the present study found that DFA resulted in improved analgesia compared with that provided by sufentanil in patients following CRC resection. It is hypothesized that the possible reason for this could be that flurbiprofen axetil inhibits cyclooxygenase enzymes to reduce prostaglandin levels, which subsequently alleviates pain and improves the pain threshold (24), while dezocine activates μ-opioid receptors to relieve pain, and suppresses noradrenaline reuptake to restrain pain transmission (13). By contrast, sufentanil only activates the μ-opioid receptor to provide an analgesic effect (32). Therefore, DFA exerts both central and peripheral analgesic effects, whereas sufentanil only provides central analgesia. This dual action of DFA may provide superior analgesic outcomes than those of sufentanil in patients following CRC resection. Additionally, previous studies have indicated that flurbiprofen axetil plus opioids provide increased patient satisfaction compared with that provided by opioids in patients after surgery (25,27). In the present study, patient satisfaction following DFA treatment was improved compared with that following sufentanil treatment in patients after CRC resection, which is consistent with the previous studies (25,27). This may be attributed to the alleviation of postoperative pain by DFA being more effective than that of sufentanil, and pain being negatively associated with satisfaction in patients after surgery (33,34). Consequently, postoperative analgesia and patient satisfaction in the patients treated with DFA were elevated compared with those in the patients treated with sufentanil following CRC resection.

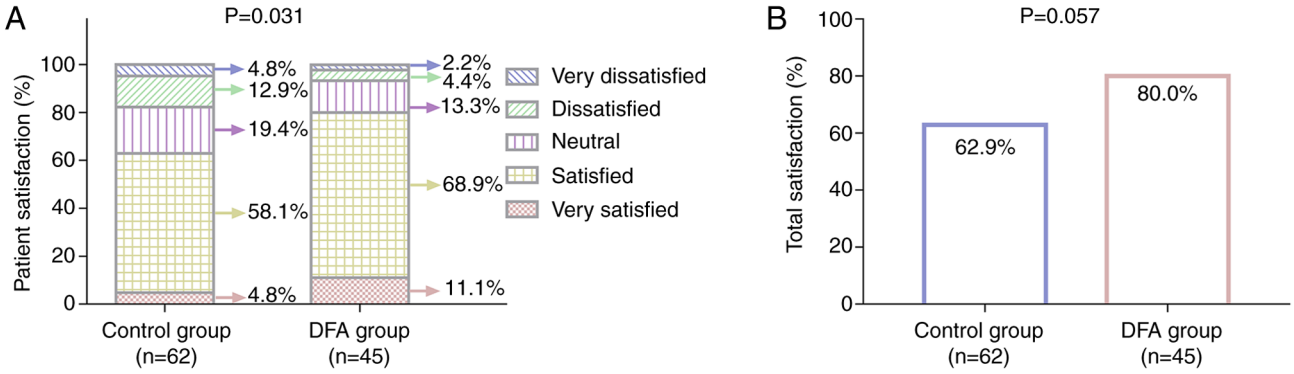

Figure 4. Patient satisfaction in the DFA group is greater than that in the control group. Comparison of (A) patient satisfaction ratings and (B) the percentage of patients reporting total satisfaction between the DFA and control groups. DFA, dezocine plus flurbiprofen axetil.

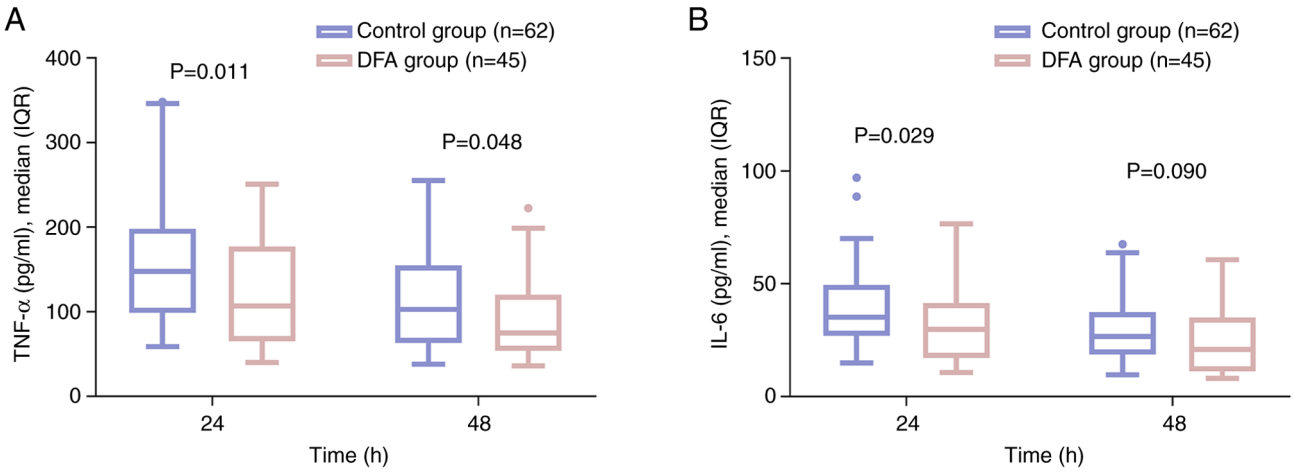

Figure 5. Levels of TNF-α at 24 and 48 h in addition to IL-6 levels at 24 h are reduced in the DFA group compared with those in the control group. Comparison of (A) TNF-α and (B) IL-6 levels at 24 and 48 h between the DFA and control groups. TNF-α, tumor necrosis factor-α; IL-6, interleukin 6; DFA, dezocine plus flurbiprofen axetil; IQR, interquartile range.

Previously, studies have reported reductions in postoperative circulating TNF-α and IL-6 levels in patients receiving flurbiprofen axetil plus opioids (25,35,36). Consistent with this, the present study showed that DFA decreased the levels of TNF-α and IL-6 compared with those in patients treated with sufentanil following CRC resection, suggesting that DFA had a superior anti-inflammatory effect in these patients. However, pro-inflammatory cytokines, including TNF-α and IL-6, activate nociceptor terminals, triggering inflammatory pain and sensitizing the nociceptors, which lowers the pain threshold and contributes to postoperative pain (23,37). Therefore, the improved analgesic effect of DFA compared with that of sufentanil in patients after CRC resection might be that the reduction of pro-inflammatory cytokine levels by DFA reduced inflammatory pain and attenuated the lowering of the pain threshold (23).

Both opioids and nonsteroidal anti-inflammatory drugs exhibit adverse effects on the gastrointestinal tract (38,39). Previous studies have reported that the adverse events of flurbiprofen axetil plus opioids include nausea, pruritus, vomiting, dizziness and drowsiness in patients undergoing gastrointestinal surgery (40-42). The present study did not identify any novel or unexpected events in the patients who received DFA after CRC resection. In addition, the incidence of adverse events did not differ between the patients who received postoperative DFA and those who received sufentanil, consistent with previous studies (25,43). These findings suggest that the safety profile of DFA is acceptable in patients after CRC resection.

However, there were some limitations to the current study. First, the sample size was relatively small, which weakened its statistical power. Therefore, studies with a larger sample size are warranted for validation. Second, given that sufentanil is one of the most frequently used opioids in China (12), patients receiving postoperative sufentanil in this study served as the control group. However, the analgesic effect of DFA compared with that of other opioids in patients after CRC resection remains uncertain and requires further investigation. Third, PCA was used in the present study and the results might not be applicable to other administration methods, such as intravenous injection. Thus, the analgesic effect of DFA using other administration methods remains to be investigated. Fourth, randomization was unable to be performed in this study, which could have introduced selection bias and limited the generalizability or reliability of these findings. Therefore, future randomized, controlled studies are required for validation.

In conclusion, the postoperative administration of DFA exhibits an improved analgesic effect, improves patient satisfaction and reduces the levels of pro-inflammatory cytokines compared with those of sufentanil in patients following CRC resection, but has comparable adverse effects. These findings provide evidence for the application of DFA as an analgesic option in with patients with CRC following resection of the tumor. However, future studies with a larger sample size and other administration methods are warranted to validate the analgesic effect of DFA.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

JH designed the study. Material preparation, data collection and analysis were performed by SY and JH. The first draft of the manuscript was written by SY and both authors commented on previous versions of the manuscript. SY and JH confirm the authenticity of all the raw data. Both authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The study received approval from the Ethics Committee of Lishui Hospital of Zhejiang University (Lishui, China; approval no., 2017056). All patients provided written informed consent.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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