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ORIGINAL RESEARCH

Comparison of systemic morphine, nalbuphine, and epidural analgesia on acute and chronic postoperative pain in laparoscopic colorectal surgery: a randomized controlled trial

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Abstract

This study aimed to assess the effectiveness of diverse postoperative analgesic techniques in laparoscopic colorectal surgery and ascertain whether systemic administration of nalbuphine is a suitable alternative for this type of procedure. Sixty-nine patients suffering from colorectal cancer and undergoing laparoscopic surgery were randomly divided into three groups (n = 23, per group). Group R received patient-controlled epidural analgesia (PCEA) with ropivacaine. Group M received patient-controlled intravenous analgesia (PCIA) with morphine. Group N received PCIA with nalbuphine. Pain at rest (PAR), movement-evoked pain (MEP), stress hormone and any complications during the 72 hours after surgery were recorded. Additionally, chronic post-surgical pain (CPSP) at 3 months and 6 months were also recorded. There was no significant difference in PAR among the 3 groups. However, patients in Group N had a higher intensity of MEP compared to those in Group R after surgery ($p < 0.05$). There was no significant difference in CPSP at 6 months among the 3 groups ($p > 0.05$), but the incidence of CPSP at 3 months was higher in Group N ($p = 0.01$, as compared to Group R). The occurrences of pruritus and postoperative nausea and vomiting (PONV) were observed to be considerably greater in Group M as compared to the other two groups ($p < 0.05$). In conclusion, PCEA is more effective than PCIA with nalbuphine in reducing postoperative MEP and CPSP at 3 months after laparoscopic colorectal surgery. However, there was no significant difference between PCEA and PCIA with nalbuphine in reducing CPSP at 6 months. Although morphine and nalbuphine have the similar analgesic effects, morphine is associated with more side effects. Therefore, PCIA with nalbuphine might be a good option for patients who are not suitable for PCEA or have a high risk for PONV or pruritus.

Keywords

Postsurgical pain; Complication; Epidural analgesia; Nalbuphine; Morphine; Colorectal surgery

1. Introduction

Colorectal cancer holds the third position globally and second in China concerning the prevalence of malignancy [1, 2]. According to estimates, there were around 152,810 new cases of colorectal cancer in the United States in 2024 [3]. To reduce surgical stress and trauma, laparoscopic techniques are commonly used in colorectal cancer surgery. However, even with these techniques, patients still experience gastrointestinal complications and pain after the surgery. Postoperative pain can cause stress and trigger more gastrointestinal complications, making it crucial to provide sufficient postoperative analgesia for patient recovery.

After colorectal cancer surgery, patients may experience two types of pain including incision pain and visceral pain. Incision pain can be either pain at rest (PAR) or movement-evoked pain (MEP). Currently, PAR draws much more attention than MEP, but the latter may result in poor outcomes [4], such as postoperative atelectasis, thromboembolism and postoperative functional impairment. The International Association for the Study of Pain has designated 2020 as the Global Year for the Prevention of Pain. Chronic postsurgical pain (CPSP) is a condition that has been getting a lot of attention, and anesthesiologists play a critical role in managing it [5]. Adequate perioperative analgesia, control of acute postoperative pain, and early ambulation, mobilization and rehabilitation can help address CPSP [6]. Failure to manage postoperative pain effectively can result in chronic postsurgical

pain and negatively impact the patient's quality of life [7]. Therefore, controlling acute postoperative pain is the most effective approach [8].

Postoperative pain management in colorectal cancer surgery commonly involves the use of either epidural analgesia or systemic analgesia using morphine. Compared to systemic opioids, epidural analgesia provides better pain relief regardless of catheter placement [9], and it also reduces the risk of chronic postsurgical pain [10]. However, epidurals can result in rare but serious complications that need to be taken into account. An alternative option is nalbuphine, which is κ-receptor agonist and μ-receptor antagonist that provides effective pain relief with fewer side effects [11–13]. Preemptive administration of nalbuphine has been shown to be safe and effective in reducing postoperative pain [14]. As far as we are aware, there have been limited investigations into the impact of nalbuphine on CPSP. We suppose systemic nalbuphine is equally efficacious in managing acute and chronic postoperative pain, with fewer adverse effects compared to systemic morphine and epidural analgesia coupled with local anesthetics following laparoscopic colorectal surgery. Hence, the objective of this investigation is to contrast the effectiveness of diverse postoperative analgesic methodologies in laparoscopic colorectal surgery while ascertaining the suitability of systemic nalbuphine as a good option for such surgical procedures.

2. Patients and methods

2.1 Participants

A total of 100 patients who underwent laparoscopic colorectal cancer radical resection were recruited, and 69 patients were eventually enrolled in the study. These patients were divided into three groups: Group R (n = 23) received patient-controlled epidural analgesia (PCEA) with ropivacaine; Group M (n = 23) was administered patient-controlled intravenous analgesia (PCIA) with morphine; and Group N (n = 23) received nalbuphine via PCIA. The study included patients who were over 18 years of age and had an American Society of Anesthesiologists (ASA) physical status of I–III. Patients with a history of chronic pain, addiction to painkillers, contraindications to epidural block, allergies to morphine, nalbuphine or ropivacaine, and hepatic or renal dysfunction were excluded from the study.

The participants were assigned randomly to one of three groups using a computer-generated randomization table. In total, 61 patients completed the study (21 in Group R, 20 in Group M and 20 in Group N). Eight patients were excluded from this trial, 2 from Group R, 3 from Group M and 3 from Group N. The reasons for exclusion from the analysis included failed epidural puncture in 1 patient, failure of the PCEA pump line in 1 patient, changed surgical procedures in 3 patients, mechanical failure of the PCA pump in 1 patient, and loss to follow-up in 2 patients. The flow chart of the study is shown in Fig. 1. Data collection and the final analysis were conducted at three primary time points, which were 72 hours (P72H), 3 months (P3M) and 6 months (P6M) after the operation.

2.2 Study protocol

No pre-operative medication was administered to any of the patients. Upon admission to the operating room, the patient had a peripheral venous catheter inserted to allow for fluid infusion. Additionally, their electrocardiogram (ECG), blood pressure (BP), heart rate (HR), and pulse oxygen saturation (SpO_2) were routinely monitored. Midazolam 0.05 mg/kg, sufentanil 0.3 μg/kg, propofol (TCI 2.5–4.5 μg/mL), and vecuronium 0.12 mg/kg were administered for the induction of general anaesthesia. Propofol (2–3 μg/mL) and remifentanil (2–4 ng/mL) in TCI mode were applied for the maintenance of general anaesthesia, sufentanil 5–10 μg was administered when necessary, and vecuronium was incrementally administered under the guidance of a neuromuscular monitor. Bispectral index (BIS) was maintained at 40–55, partial pressure of end-tidal carbon dioxide ($PetCO_2$) at 35–40 mmHg, and nasopharyngeal temperature at 36–37 °C during anaesthesia. The urinary output was more than 1 mL/kg/h, and fluid was administered at 10 mL/kg/h. When stroke volume variation (SVV) more than 13%, 150 mL fluid was administered. Another 150 mL fluid was given when necessary, and ephedrine was administered when hypotension developed (SBP decreased more than 20% from baseline). In all 3 groups, sufentanil 0.1 μg/kg was administered 30 min before surgery ended, and atropine 0.02 mg/kg and neostigmine 0.04 mg/kg were used to reverse muscular relaxation. The duration of surgery and anaesthesia, the volume of fluid infusion and bleeding, and opioid dosage were recorded.

Patients in Group R had epidural puncture and catheterization performed before the induction of general anesthesia. A loading of 5 mL of 0.2% ropivacaine was initiated as soon as the end of surgery, and continuously infusion 0.2% ropivacaine at a rate of 6 to 8 mL/h, with a bolus of 3 mL allowed every 30 min, according to the standard practice in our hospital. In Groups M and N, patients received morphine (0.5 mg) or nalbuphine (1 mg) on demand, respectively, with a lockout period of 5 minutes.

After surgery, patients were monitored for pain using a numeric rating scale (NRS) score. If the score for PAR was 4 or higher, it was considered insufficient analgesia. In such cases, patients in Group R received 5 mL of 0.2% ropivacaine epidurally. If the ropivacaine was not effective, patients were given intravenous morphine and excluded from the trial. Patients in Group M or Group N were given morphine 1–2 mg or nalbuphine 2–4 mg, respectively. If the medication was still not effective, it was given a second time, and the pump was reset so that the NRS score for PAR was less than or equal to 3. The NRS scale spanned from 0 to 10 points, with a score of 0 indicating an absence of pain, while scores between 1 and 3 represented mild pain. Scores ranging from 4 to 6 reflected moderate levels of pain, whereas those falling within the range of 7–10 denoted severe pain.

2.3 Outcome measures

Primary outcomes: the incidence of CPSP at 3 months and MEP.

After surgery, patients were transferred to the post-anesthesia care unit after surgery for emergency care. The

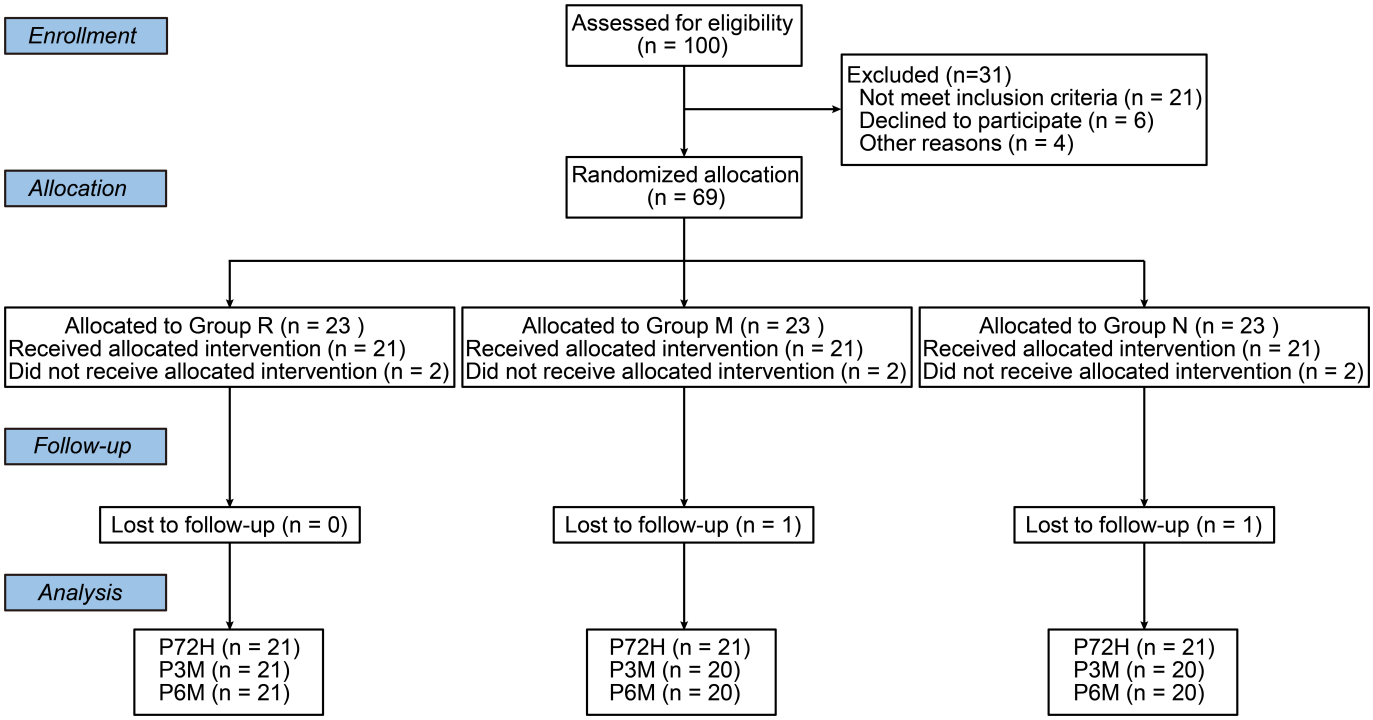

FIGURE 1. Consort flow diagram. P72H, 72 hours post-operatively; P3M, 3 months post-operatively; P6M, 6 months post-operatively.

NRS was used to evaluate PAR and MEP at the following time intervals: 5 min after extubation and 24, 48 and 72 hours after surgery. In this study, MEP referred to coughing-evoked pain. CPSP was evaluated using the NRS and was defined as the pain related to surgery that patients could feel in daily life (NRS score equal to or greater than 1), even three months after surgery or longer. The incidence of CPSP at 3 months and 6 months after surgery were collected through telephone follow-up, and the worst pain intensity experienced by patients during the week prior to the survey was recorded too. The investigators who conducted the postoperative and extended-term follow-ups were neither involved in the administration of anesthesia nor were informed about randomization.

Secondary outcomes: PAR, CPSP at 6 months, the intensity of CPSP, plasma levels of cortisol (Cor) and adrenocorticotropic hormone (ACTH) within 72 h after surgery, pruritus, postoperative nausea and vomiting (PONV), and time to the first flatus after surgery.

Venous blood samples were collected at the following time points: on the morning of the surgery, at the end of surgery, and on the morning of postoperative Days 1 and 3. The plasma levels of Cor and ACTH were measured using chemiluminescence. The pruritus and PONV within 48 hours after surgery and the time to the first flatus after surgery were recorded. Additionally, surgical complications such as anastomotic leakage, ileus and surgical site infection were recorded by reviewing cases.

2.4 Statistical analysis

The sample size was calculated basing on the data of the incidence of CPSP at 3 months that was measured in 15 patients in a preliminary analysis. The incidence of CPSP at 3 months after surgery was 20%, 20% and 60%, respectively. To achieve a study power of 80%, with a 5% alpha error, a total sample size of 61 participants was needed. Allowing for a 10% rate of incomplete follow-up or dropout, at least 69 patients were required in this study.

The statistical analysis was performed using SPSS software (version 25.0, IBM Corp, Armonk, NY, USA). To check the normality of distributions, the Shapiro-Wilk test was used. Patient characteristics data were analysed using one-way analysis of variance (ANOVA) or the χ^2 test. The intensity of PAR and MEP is presented as the median and interquartile range, while CPSP and postoperative complications data are presented as frequencies (%). The data on Cor and ACTH levels and the time to first flatus are presented as the mean $\pm$ standard deviation (SD).

The intensity of PAR, MEP and CPSP was analyzed using the nonparametric Kruskal-Wallis test. The incidence of CPSP and postoperative complications were analyzed using the χ^2 test or Fisher's exact test. Meanwhile, the data analysis on Cor and ACTH levels was done using two-way repeated-measures ANOVA followed by Bonferroni *post hoc* test. The data on the time to the first flatus was performed using one-way ANOVA followed by Bonferroni *post hoc* test. For the correlation analysis between the intensity of MEP and CPSP, Fisher's exact test was utilized. A value of $p < 0.05$ was considered statistically significant.

3. Results

There were no significant differences in demographic and clinical characteristics among the 3 groups (Table 1). One case in group M underwent reoperation for ileus.

The intensity of PAR and MEP were evaluated using the

TABLE 1. The demographic and clinical characteristics of patients.

	Group R	Group M	Group N	*p* value
Age (yr)	60 ± 10	62 ± 9	58 ± 9	0.503
BMI (kg/m^2)	24 ± 3	24 ± 2	23 ± 3	0.563
Sex (male/female)	16/5	13/8	16/5	0.497
ASA (I~II/III)	15/6	13/8	11/10	0.446
History of alcoholism	7/14	3/18	4/17	0.409
History of operation	5/16	6/15	4/17	0.769
Surgical approach (miles/others)	3/18	2/19	3/18	1.000
Enterostomy	5/16	4/17	6/15	0.931
Sufentanil (μg)	57 ± 11	56 ± 9	59 ± 6	0.618
Remifentanil (mg)	1.8 ± 0.7	1.9 ± 0.6	1.8 ± 0.4	0.750
Duration of surgery (min)	233 ± 50	246 ± 60	230 ± 58	0.611
Duration of anesthesia (min)	257 ± 48	276 ± 59	257 ± 57	0.425
Infusion volume (mL)	2595 ± 618	2469 ± 331	2502 ± 366	0.652
Bleeding (mL)	58 ± 26	60 ± 24	54 ± 22	0.740
Anastomotic leakage (yes/no)	2/19	1/19	1/19	1.000
Surgical site infection (yes/no)	2/19	3/17	2/18	0.890
Radiation before or after surgery (yes/no)	3/18	4/16	3/17	0.914
Chemotherapy before or after surgery (yes/no)	10/11	9/11	11/9	0.854

Notes: Values are presented as mean ± SD or absolute value (n); Group R, PCEA with ropivacaine; Group M, PCIA with morphine; Group N, PCIA with nalbuphine. BMI, body mass index; ASA, American society of anesthesiologists.

NRS at four different time points: 5 min after extubation (t1) and 24 h (t2), 48 h (t3) and 72 h (t4) after the surgery. There was no patient excluded from Group R due to insufficient effectiveness of epidural analgesia. The non-parametric Kruskal-Wallis test was used for the intensity of PAR and MEP. No discrepancies in the magnitude of PAR were observed among the three groups within the 72-hour postoperative period (Fig. 2A). Patients in Group N had a significant higher intensity of MEP than those in Group R during the 72 hours after surgery ($p < 0.01$). However, there was no significant difference neither between Group R and Group M nor between Group M and Group N ($p > 0.05$) (Fig. 2B).

The incidence of postoperative complications, including CPSP at 3 and 6 months after surgery, and pruritus and PONV within the first 48 hours after surgery, were analyzed using Fisher's exact test. The results showed that the incidence of CPSP was higher in Group N compared to Group R at 3 months after surgery ($\chi^2 = 6.567$, $p = 0.01$). However, there was no difference between Group R and Group M or between Group M and Group N. No significant difference was found among the three groups at 6 months after surgery ($p > 0.05$) (Table 2). The occurrences of pruritus and PONV were notably greater in Group M compared to both Group R and Group N following pairwise comparison ($p < 0.05$). However, there was no difference between Group R and Group N ($p > 0.05$) (Table 2). The pain intensity of CPSP at 3 months was analyzed using non-parametric Kruskal-Wallis test. There was no significant difference among the three groups ($p > 0.05$) (Table 3). At 6 months after surgery, only one patient in Group N experienced moderate pain, while the remaining patients with CPSP reported mild pain.

In patients who experienced mild or moderate-severe MEP, the incidence of CPSP at 3 months was 4.5% and 33.3%, respectively. The Spearman correlation was 0.329 ($p = 0.011$), and the incidence of CPSP at 3 months was significantly increased in patients who experienced moderate-severe MEP. However, there was no significant difference in the incidence of CPSP at 6 months in patients who experienced mild or moderate-severe MEP ($p > 0.05$), as shown in Table 4.

ACTH and Cor data were collected on the morning of the surgery (T1), at the end of the surgery (T2), and in the morning of postoperative Days 1 (T3) and 3 (T4). Two-way repeated-measures ANOVA was used to analyse the levels of ACTH and Cortisol. The results showed that the interaction of the group × time had no statistically significant effect on either ACTH or Cor levels. Therefore, the main effect of the group or time factor on ACTH and Cor were analyzed respectively. There were no differences in ACTH ($F = 0.228$, $p = 0.797$) and Cor ($F = 0.109$, $p = 0.997$) among the three groups. The time factor had a statistically significant impact on ACTH concentration ($p = 0.013$). After pairwise comparison, it was found that there was a significant difference between T1 and T2 ($p = 0.008$) with mean difference (MD) 2.752 (95% confidence interval (CI): 0.590–4.913), but there were no differences among the other time points ($p > 0.05$) (Fig. 3A). However, there were no differences in the level of Cor among the different time points

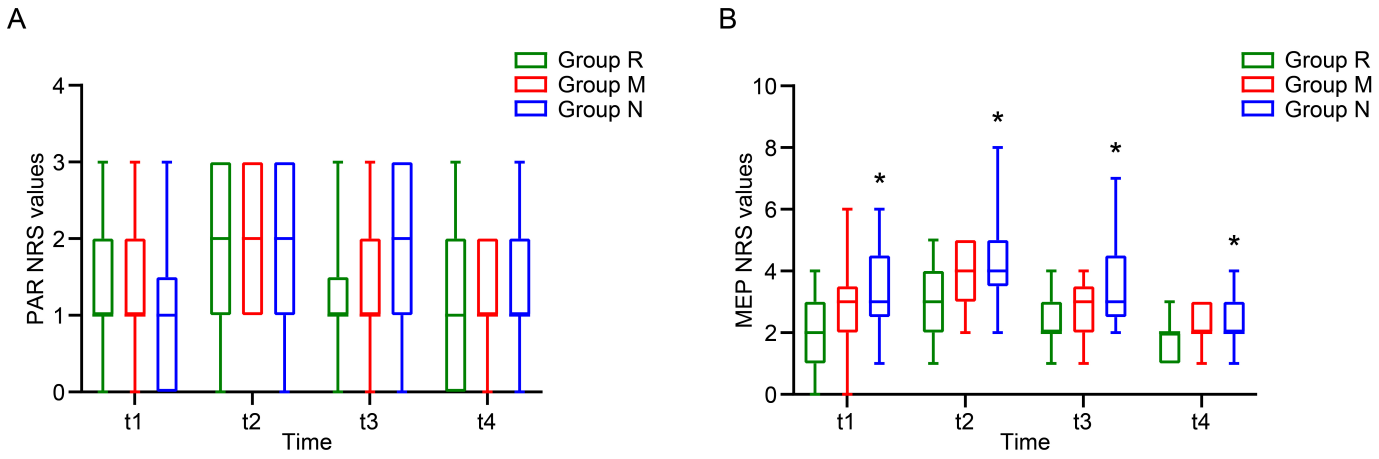

FIGURE 2. The intensity of PAR and MEP among the 3 groups during 72 hours after surgery. (A) The intensity of PAR. (B) The intensity of MEP. Notes: Group R, PCEA with ropivacaine; Group M, PCIA with morphine; Group N, PCIA with nalbuphine. PAR and MEP were evaluated using NRS at the following time points: 5 min after extubation (t1), 24 h (t2), 48 h (t3) and 72 h (t4) after surgery. The boxes represent the median and the bars represent the interquartile range. *$p < 0.05$, refers to the difference between the group R and group N. PAR, pain at rest; NRS, numeric rating scale; MEP, movement-evoked pain.

TABLE 2. Postoperative complications in the 3 groups.

Complications	Group R	Group M	Group N	χ^2	p Value
CPSP P3M	2 (9.5)	3 (15)	9 (45)*	7.520	0.017
CPSP P6M	1 (4.8)	2 (10)	5 (25)	3.469	0.151
Pruritus	1 (4.8)	8 (38.1)$^{\#}$	1 (4.8)$^{\&}$	9.883	0.004
PONV	1 (4.8)	8 (38.1)$^{\#}$	1 (4.8)$^{\&}$	9.883	0.004

*Notes: Values are presented as frequencies (%); Group R, PCEA with ropivacaine; Group M, PCIA with morphine; Group N, PCIA with nalbuphine. *$p < 0.05$, Group N vs. Group R; $^{\#}p < 0.05$, Group M vs. Group R; $^{\&}p < 0.05$, Group M vs. Group N. CPSP, chronic postsurgical pain; PONV, postoperative nausea and vomiting; P3M, 3 months post-operatively; P6M, 6 months post-operatively.*

TABLE 3. Pain intensity of CPSP at 3 and 6 months in the 3 groups.

Pain intensity	Group R	Group M	Group N	H	p Value
P3M	n = 2	n = 3	n = 9	0.413	0.814
Mild (n)	1	1	5		
Moderate (n)	1	2	4		
Severe (n)	0	0	0		
P6M	n = 1	n = 2	n = 5		NA
Mild (n)	1	2	4		
Moderate (n)	0	0	1		
Severe (n)	0	0	0		

Notes: Values are presented as number (n). Group R, PCEA with ropivacaine; Group M, PCIA with morphine; Group N, PCIA with nalbuphine. P3M, 3 months post-operatively; P6M, 6 months post-operatively. NA, not applicable. The NRS scores range from 1 to 3, representing mild pain, 4 to 6 representing moderate pain, and 7 to 10 representing severe pain.

($p > 0.05$), as shown in Fig. 3B.

The data on the time to the first flatus after surgery was performed using One-way ANOVA followed by Bonferroni *post hoc* test. Compared with Group R (34.0 ± 16.3 h), the time to the first flatus was longer in Group M (49.0 ± 18.6 h) or Group N (53.9 ± 21.9 h) after pairwise comparison (p = 0.035 and p = 0.004, respectively), but there was no significant difference between Group M and Group N ($p > 0.05$).

4. Discussion

In our study, we discovered that both epidural analgesia and systemic morphine or nalbuphine could provide equal relief for postoperative acute pain when the patient is resting and CPSP 6

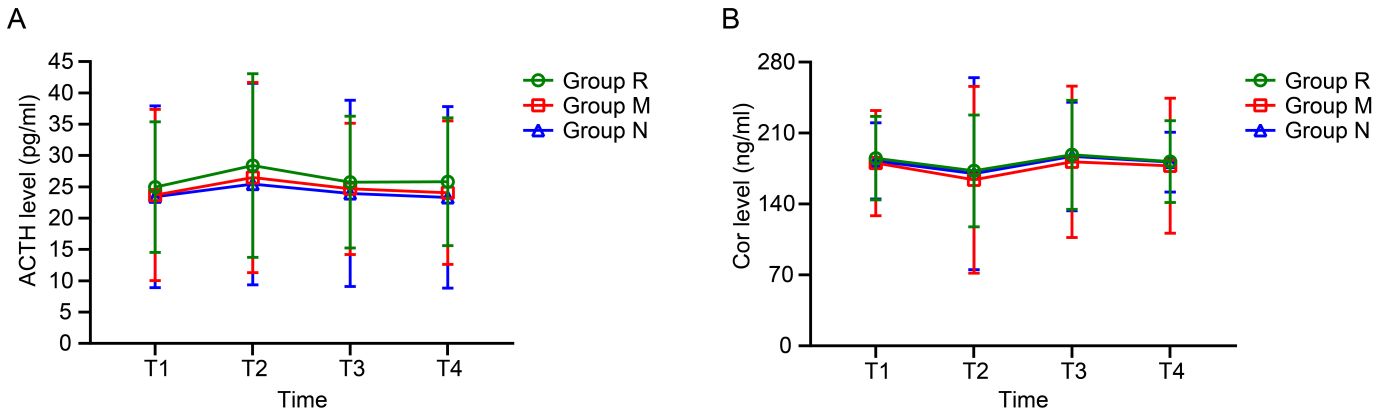

FIGURE 3. Plasma levels of ACTH and Cor among the 3 groups. (A) Plasma level of ACTH. (B) Plasma level of Cor. The curve graph represented the mean and standard deviation. ACTH and Cor data were collected on the morning of the surgery (T1, 24.95 ± 10.42 and 185.20 ± 41.22 in group R, 23.70 ± 13.69 and 180.40 ± 51.85 in group M, 23.42 ± 14.50 and 182.66 ± 37.61 in group N, respectively), at the end of the surgery (T2, 28.40 ± 14.65 and 172.67 ± 55.11 in group R, 26.48 ± 15.18 and 163.86 ± 92.13 in group M, 25.44 ± 16.09 and 170.06 ± 94.72 in group N, respectively), and on the morning of postoperative Days 1 (T3, 25.75 ± 10.52 and 188.57 ± 53.72 in group R, 24.68 ± 10.48 and 181.62 ± 74.73 in group M, 23.96 ± 14.86 and 186.95 ± 53.50 in group N, respectively) and Days 3 (T4, 25.82 ± 10.21 and 181.98 ± 40.38 in group R, 24.07 ± 11.45 and 177.75 ± 66.56 in group M, 23.32 ± 14.50 and 181.40 ± 29.52 in group N, respectively). ACTH, adrenocorticotropic hormone.

TABLE 4. Correlation of MEP and CPSP (n (%)).

	MEP		*p* value
	Mild	Moderate-severe	
CPSP P3M			
CPSP n = 14 (%)	1 (4.5)	13 (33.3)	$p = 0.011$
No CPSP n = 47 (%)	21 (95.5)	26 (66.7)	$p = 0.011$
CPSP P6M			
CPSP n = 8 (%)	1 (4.5)	7 (17.9)	$p = 0.239$
No CPSP n = 53 (%)	21 (95.5)	32 (82.1)	$p = 0.239$

Notes: Values are presented as frequencies (%). MEP, movement-evoked pain; CPSP, chronic postsurgical pain; P3M, 3 months post-operatively; P6M, 6 months post-operatively.

months after the procedure. However, we observed that epidural analgesia was more effective than systemic nalbuphine in attenuating postoperative acute pain when the patient is moving and reducing the incidence of CPSP at 3 months after the procedure. Epidural analgesia and systemic analgesia are commonly used for postoperative pain management after intra-abdominal surgery [15]. However, in minimally invasive surgery, there is no conclusive evidence showing that epidural analgesia is superior to systemic analgesia in terms of long-term prognosis. Morphine, a potent agonist for μ-opioid receptors, is widely used in Europe and North America. It is hydrophilic, and its metabolite, morphine-6-glucuronic acid, is even more effective in providing pain relief. On the other hand, nalbuphine [16] is a semisynthetic opioid analgesic that works as both a mixed μ-receptor antagonist and κ-receptor agonist. It has a weak affinity for δ-receptors but is still as effective as morphine in providing pain, with fewer adverse effects.

According to a Cochrane review, an epidural technique is more effective in providing pain relief than PCIA [17]. The difference in pain relief efficacy is minor at rest, but more significant during movement. Studies have shown that the intensity of MEP can be up to twice as high as that of PAR [18]. Since MEP is commonly experienced during normal activities such as breathing, coughing, and walking, it can have a significant negative impact on function and postoperative recovery than PAR [4]. Therefore, it is essential to focus more on MEP when providing postoperative pain management.

An epidemiological survey conducted in China to study the incidence of CPSP after colorectal surgery revealed that the overall incidence of CPSP at 3 months was 32.1% [19], which is higher compared to the results of our study. We believe that different surgical approaches and analgesia strategies may be the reasons for this difference. Our study showed that the stronger the intensity of acute MEP patients experienced, the higher the risk of developing CPSP at three months. This leads us to speculate that MEP might play a role in the development of CPSP. We observed that better MEP control in the epidural group could be attributed to the lower incidence of CPSP at three months than that in the nalbuphine group.

In this study, we observed that there were no notable differences in ACTH or Cor levels among the three groups. This suggested that the perioperative stress experienced by the patients in all three groups was similar to some extent. One possible explanation for this could be that there were no differences in PAR among the three groups, and the venous blood samples were collected for ACTH and Cor while the patients were at rest.

However, we found that the incidence of pruritus and PONV was significantly higher in the morphine group as compared

to the epidural group or the nalbuphine group. Additionally, the epidural group had a shorter time to the first flatus after surgery when compared to the systemic morphine or systemic nalbuphine.

The exact cause of pruritus is not fully understood, although it is known that the μ-receptor plays a major role in producing itch, while the κ-receptor has the opposite effect. To treat opioid-induced pruritus, it is recommended to use nalbuphine as a first-line treatment [20]. Prophylactic administration of nalbuphine has been shown to reduce the incidence and severity of pruritus without affecting sedation or the analgesic effects of opioids [21].

Gastrointestinal paralysis, nausea and vomiting and pain are common complications after abdominal surgery. While the exact mechanisms behind opioid-induced nausea and vomiting (OINV) are not fully understood, it is believed that the stimulation of chemoreceptor trigger zones, vestibular apparatus and gastrointestinal tract receptors play a major role. Opioids can directly stimulate the vestibular apparatus through μ-receptor activation. The μ-receptor agonists mainly increase gastric emptying time and inhibit gastrointestinal motility, which contributes to OINV [22]. According to a multicenter study, preemptive administration of nalbuphine resulted in lower incidence of PONV [15]. This effect is due to its activity as a central antagonist on μ-receptors [23]. Several studies have demonstrated that the nalbuphine provides similar analgesic efficacy as morphine, but with a better safety profile for PONV and pruritus [11, 24], which is consistent with findings of our study.

It was found the time to the first flatus was shorter in PCEA as compared to the morphine group or nalbuphine group, which suggested that epidural analgesia could promote gastrointestinal function recovery after laparoscopic colorectal surgery. The results of 22 trials including 1138 participants showed that an epidural containing a local anaesthetic would decrease the time required for return of gastrointestinal transit as measured by the time to first flatus after an abdominal surgery [25]. A blockade of sympathetic gut innervation creating a relative parasympathetic predominance may be one of the reasons. Systemic nalbuphine didn't improve postoperative gastrointestinal recovery after laparoscopic surgery [26], which is consistent with our findings.

In this study, it was found that both epidural analgesia and systemic morphine or nalbuphine can provide the same level of pain relief for acute postoperative pain when the patient is at rest. However, epidural analgesia was found to be more effective than systemic nalbuphine in reducing acute pain caused by movement and chronic pain after 3 months, while also helping the patient recover faster gastrointestinal function. Based on these findings, we believe that epidural analgesia could be a better option for patients undergoing laparoscopic colorectal cancer surgery. However, it was not recommended to use thoracic epidural analgesia as part of ERAS (Enhanced Recovery After Surgery) pathways in laparoscopic colorectal surgery by Hubner [27] and Gustafsson [28], as it appears to have a high failure rate (ranging between 12% and 32%) and delay medical recovery. The delay may be due to a higher risk of hypotension (OR, 9.94; 95% CI, 3.17–31.19), urinary retention (OR, 1.60; 95% CI, 1.02–2.51) or motor blockade (OR, 12.7; 95% CI, 5.26–32.5) requiring additional postoperative care compared with PCIA. Additionally, possible alternative co-analgesic techniques could provide similar analgesia. In our study, the primary outcome was chronic postsurgical pain at 3 months which was better controlled with epidurals. Different endpoints contributed to different conclusions, which may be one of the reasons why results vary. However, more high-quality and large sample clinical trials are needed in the future to provide better insights.

There are a few limitations in our study that should be addressed. Firstly, in the epidural analgesia group, the epidural puncture and catheterization procedures had to be conducted before the general anaesthesia in the operation room, which made it impossible to implement a double-blind rule. Secondly, the study's sample size was limited, and further research is needed to confirm and verify the results. Thirdly, patients' quality of life after colorectal surgery is decided by postoperative complications, pain, and metastasis. However, in our study, we only investigated the effects of analgesia strategies on postoperative complications and pain. Therefore, the effects of various analgesia strategies on postoperative metastasis need to be tested and examined in the future.

5. Conclusions

Due to limited sample size, the conclusions of this study should be drawn with cautious. PCEA is more effective than PCIA with nalbuphine in reducing the intensity of postoperative MEP and the incidence of CPSP at 3 months following laparoscopic colorectal surgery. However, at 6 months, there was no significant difference between the two methods. Since PCEA is an invasive procedure with a certain failure rate and rare but potentially serious complications, PCIA with morphine could be considered as an alternative to achieve equal acute and chronic pain control. Although morphine and nalbuphine have the similar analgesic effects, morphine is associated with more side effects. Therefore, PCIA with nalbuphine also might be a good option for patients who are not suitable for PCEA or have a high risk for PONV or pruritus.

ABBREVIATIONS

CPSP, chronic postsurgical pain; MEP, movement-evoked pain; PAR, pain at rest; PCEA, patient-controlled epidural analgesia; PCIA, patient-controlled intravenous analgesia; Cor, cortisol; ACTH, adrenocorticotropic hormone; ASA, American society of anesthesiologists; NRS, numeric rating scales; BIS, Bispectral index; SVV, stroke volume variation; PONV, postoperative nausea and vomiting; BMI, Body Mass Index; OINV, opioid-induced nausea and vomiting; ECG, electrocardiogram; BP, blood pressure; HR, heart rate; SpO_2, pulse oxygen saturation; $PetCO_2$, partial pressure of end-tidal carbon dioxide; ANOVA, analysis of variance; MD, mean difference; CI, confidence interval.

AVAILABILITY OF DATA AND MATERIALS

The datasets used and analyzed during the current study are available from the corresponding author on any reasonable request.

AUTHOR CONTRIBUTIONS

YJ—performed data analysis, wrote and revised the manuscript. XLL—performed anesthesia and collected the intraoperative data. SFS—performed postoperative follow-ups and collected the postoperative data. QC—performed data analysis. HLL—designed this trial protocol and revised the manuscript. All authors reviewed and approved the final version of the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This prospective, randomized study was approved by the ethics committee of Chongqing University Cancer Hospital (Reference number: 2017-002) and registered at https://www.chictr.org.cn/ (registration No: ChiCTR-INR-17011092) on 08 April 2017. The informed consent was obtained from each patient before the trial. We confirm that all methods were carried out in accordance with relevant guidelines and regulations.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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