Original Article

Effects of Preoperative Extended-release Dinalbuphine Sebacate as an Analgesia in Ileostomy Reversal: A Randomized, Open-label Study

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Key Words
Dinalbuphine sebacate;
Ileostomy reversal;
Morphine;
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Purpose. Analgesia following stoma takedown is an essential postoperative management step because it is associated with recovery, complications, and patient satisfaction. Dinalbuphine sebacate (DS) is a novel long-acting analgesic. This open-label, randomized study investigated the efficacy and safety of DS as an analgesia following ileostomy reversal.
Materials and Methods. Patients who had undergone laparoscopic surgery and been scheduled to receive ileostomy reversal were equally randomized into DS and control groups. In the DS group, patients were intragluteally injected with a single dose of 150 mg/2 mL DS 12 hours before surgery. In both groups, fentanyl was administered as required in the postoperative recovery room; in wards, opioids and ketorolac were administered for breakthrough pain whose numerical rating scale (NRS) ≥ 4 and < 4, respectively.
Results. Thirty-eight patients completing all assessments were analyzed. The primary endpoint, mean fentanyl consumption, was significantly lower in the DS group (13.8 ± 27.5 μg vs. 36.1 ± 38.6 μg, $p = 0.045$). No significant difference was observed in morphine, nalbuphine, and ketorolac amounts administered in wards between the groups. The DS group also reported a reduction in pain intensity on postoperative day (POD) 0 (3.9 vs. 4.9, $p = 0.010$) and POD 1 (1.5 vs. 2.5, $p = 0.045$) compared with the control. Since POD 2, the mean pain scores were all lower than 2.0 in both groups, without significant differences. No serious adverse reactions were observed.
Conclusions. Extended-release DS reduced the consumption of opioids and the pain intensity after ileostomy reversal surgery safely.

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Colorectal cancer (CRC) is the most commonly diagnosed malignancy in the United States and European Union.[1,2] Surgery remains the cornerstone of curative intent therapy, whether it is with ileostomy, a temporary intestinal stoma created during surgery by bringing a loop of the bowel to the abdominal surface, or not.[3,4] Although the benefit and risk of ileostomy is still a matter for debate, most countries were reported about half of patients undergoing low anterior resection adopted ileostomy. Taking the risk of anastomotic

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leakage into account, ileostomy is adopted. However, second operation, ileostomy reversal, is necessary to achieve closure subsequently. It is generally performed weeks to months after first surgery and therefore, adjunctive therapy will be obstructed.[4,5] It is essential to enhance the recovery after ileostomy reversal and then begin the next CRC therapeutic regimen immediately.

Perioperative pain management is critical because optimal pain control facilitates postoperative ambulation and rehabilitation and enhances recovery after surgery. Despite the well-known of perioperative pain management benefits, postoperative pain continues to be inadequately managed.[6] According to the guideline from the American Society of Regional Anesthesia and Pain Medicine et al., analgesics, such as acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs), and other analgesic adjuncts (e.g., ketamine and gabapentinoids) were suggested for managing postoperative pain.[7] Accordingly, guidelines for perioperative pain management recommend that physicians cautiously prescribe postoperative analgesics following gastrointestinal surgery.[8-11]

Opioids have been the mainstay treatment for acute pain in clinical settings.[12] However, opioid-sparing strategies have been implemented because opioids are addictive, occasionally leading to overdose or opioid-related adverse events (ORAEs), including respiratory depression, nausea, vomiting, and bowel dysfunction. These sparing strategies are also challenging because insufficient analgesia might cause acute pain or chronic post-surgical pain (CPSP).[13,14] Moreover, ineffective postoperative pain management can lead to physiological and psychological manifestations, resulting in prolonged hospital stay and significant economic burden.[15-17]

Long-acting dinalbuphine sebacate (DS, Naldebain® ER Injection, Lumosa Therapeutics, Taiwan) has been available in Taiwan for managing moderate-to-severe pain. DS is a prodrug of nalbuphine (opioid receptor mixed agonists/antagonists), and it has a potency similar to morphine but is associated with a lower risk of respiratory depression.[18] A randomized study showed that a single administration of DS resulted in approximately 6-day pain relief, reduced the use of postoperative ketorolac, and demonstrated a tolerable safety profile following hemorrhoidectomy.[19] Although mixed agonist-antagonist opioid analgesics were commonly considered to increase the risk of withdrawal symptoms,[20] a previous study had demonstrated that a mixture of nalbuphine and morphine administrated via intravenous patient-controlled analgesia prevented severe ORAEs and reduced morphine-related adverse reactions without withdrawal symptoms.[21]

However, few studies have reported that the effect of a long-acting mixed mu-opioid receptor (MOR) for postoperative pain control following ileostomy reversal surgeries. The present study evaluated the efficacy and safety of long-acting DS in patients undergoing ileostomy reversal compared with the standard treatment of morphine.

Materials and Methods

Study design

This was a prospective, open-label, randomized study conducted at China Medical University Hospital (CMUH), Taichung, Taiwan, from March 2019 to February 2020. All participants provided written informed consent before enrollment. This study was conducted in accordance with the Helsinki Declaration and Good Clinical Practice, approved by the Institutional Review Board of CMUH (CMUH107-REC2-110), and registered at ClinicalTrials.gov (Clinical Trials.gov Identifier: NCT03854851).

Patients

Patients who met the following criteria were enrolled: 1) aged 20-80 years, 2) had received laparoscopic surgery, 3) had been scheduled to undergo ileostomy reversal, and 4) had an American Society of Anesthesiologists physical status graded as 1-3. Exclusion criteria were 1) allergy to opioids, NSAIDs, or acetaminophen, 2) had severe complications that might affect pain assessment, 3) pregnant or breastfeeding, 4) long-term use of opioids; and 5) had ileostomy in less than 8 weeks. Eligible patients were equally ran-

domized into the DS and control groups.

Randomization list was generated with a 1:1 randomization ratio in block technology. Each randomization code was printed on opaque envelopes separately, and its assigned group was put inside. The randomization list and the envelopes were preserved by a person independent from the implement staff. While the eligibility was confirmed, the subject was allocated to the lowest available randomization code and the envelope was unsealed to check the assigned group.

Surgical procedure and perioperative management

Patients in the DS group received a single intragluteal injection of 150 mg/2 mL (extended-release) DS preoperatively (approximately 12-16 h before surgery). In both groups, fentanyl was administered if patients experienced unbearable pain in the postoperative recovery room (POR). In wards, morphine or nalbuphine was the first-line rescue medication when the pain intensity was ≥ 4. If the pain intensity was < 4 and the patient required analgesics, ketorolac was administered. In addition to the analgesic regimen, the surgical procedure and perioperative care were the same for all patients. Clear liquids were encouraged on the day of surgery. The surgery was performed under general anesthesia induced with 50-100 μg fentanyl, 40 mg lidocaine, 120 mg propofol, and 0.5-1 mg/kg rocuronium bromide; and then maintained at 1% sevoflurane during the operation. A circular incision was created around the edge of the stoma. The ileum was detached from the abdominal wall. Anastomosis was performed with side-to-side double staples. The peritoneum and fascia were closed with continuous suturing using 1-0 Vicryl. Then, the bowel was pushed back into the abdomen. The purse-string closure technique was used to close the subcutaneous layer with 2-0 monosyn. Cefmetazole was prescribed on the surgery day for prophylaxis. Acetaminophen (500 mg every 6 h) was prescribed to all patients on the first 3 days after the surgery and PRN (i.e., as required) after discharge. Patients were required to tolerate oral intake and pass flatus or stool prior to discharge.

Assessments

The primary outcome was fentanyl consumption in the POR. The secondary outcomes included analgesic consumption in wards, postoperative pain intensity from day 0 to day 7, and patient satisfaction with pain management. The pain intensity was assessed using a numerical rating scale (NRS), ranging from 0 to 10; 0 indicates no pain and 10 indicates the worst pain. A 5-point satisfaction scale, ranging from 1 to 5, was used to measure patient satisfaction on day 7 (1 means very unsatisfied and 5 means very satisfied). Concomitant medication, vital signs, adverse events, and fitness for discharge were recorded daily until discharge.

Statistical analysis

Based on the clinical experience with the use of DS, we assumed that the difference in the amounts of fentanyl consumed in POR was 20 μg, with a standard deviation (SD) of 16 μg. A total of 40 patients were considered sufficient based on a statistical power of 0.8, a Type I error at 0.05, and a drop-out rate of 10% in the two-sample two-sided test.

The efficacy outcomes were analyzed in the per-protocol population, comprising patients receiving at least one dose of the study drug and having no protocol violations. For the calculation of morphine equivalent dose (MED), the conversion ratio from fentanyl to morphine was 1:100 and from nalbuphine to morphine was 1:1. Continuous measures were analyzed using the unpaired *t* test. Categorical measures were analyzed using the chi-square test or Fisher's exact test. All tests were two-sided, and $p < 0.05$ was considered statistically significant.

Results

Patient characteristics

Forty eligible patients who underwent ileostomy reversal were enrolled and equally allocated to the DS and control groups; among these, two patients from the control group were excluded (Fig. 1). One patient

was excluded due to serious abdominal adhesion observed during surgery, and the other patient was excluded because of the willingness to receive DS postoperatively on POD 2. A total of 38 patients completed all evaluations, and their data were analyzed (Fig. 1). The majority of patients recruited into this study were diagnosed as having rectal cancer as the primary pathology. No significant differences were observed between the two groups in demographics, baseline disease characteristics, surgical time, and time to discharge (Table 1).

Efficacy outcomes

The amount of consumed postoperative analgesics is presented in Fig. 2. The mean fentanyl consumption in the POR was lower in the DS group than in the control group (13.8 ± 27.5 μg vs. 36.1 ± 38.6 μg, $p = 0.045$; Fig. 2). No significant difference was observed in the amounts of morphine, nalbuphine, and ketorolac consumed in wards between both groups (Fig. 2). The MED was slightly lower in the DS group (7.6 ± 6.2 mg vs. 10.8 ± 5 mg, $p = 0.109$). Two patients (10%) in the DS group did not require opioids for breakthrough pain after surgery.

The secondary outcome, that is, postoperative pain intensity, is summarized in Table 2 and Fig. 3. The mean NRS scores were significantly lower in the DS group than in the control group on postoperative day (POD) 0 (3.9 ± 1.2 vs. 4.9 ± 1.1, $p = 0.010$; Table 2/Fig. 3) and POD 1 (1.5 ± 0.9 vs. 2.5 ± 1.8, $p = 0.045$; Table 2/Fig. 3). Since POD 2, all the mean NRS scores were lower than 2.0 in both groups (Table 2/Fig. 3), without any significant differences (Table 2/Fig. 3).

The proportion of patients highly satisfied with postoperative pain management was higher in the DS group than in the control group (50% vs. 28%, $p = 0.198$). No patient was unsatisfied or highly unsatis-

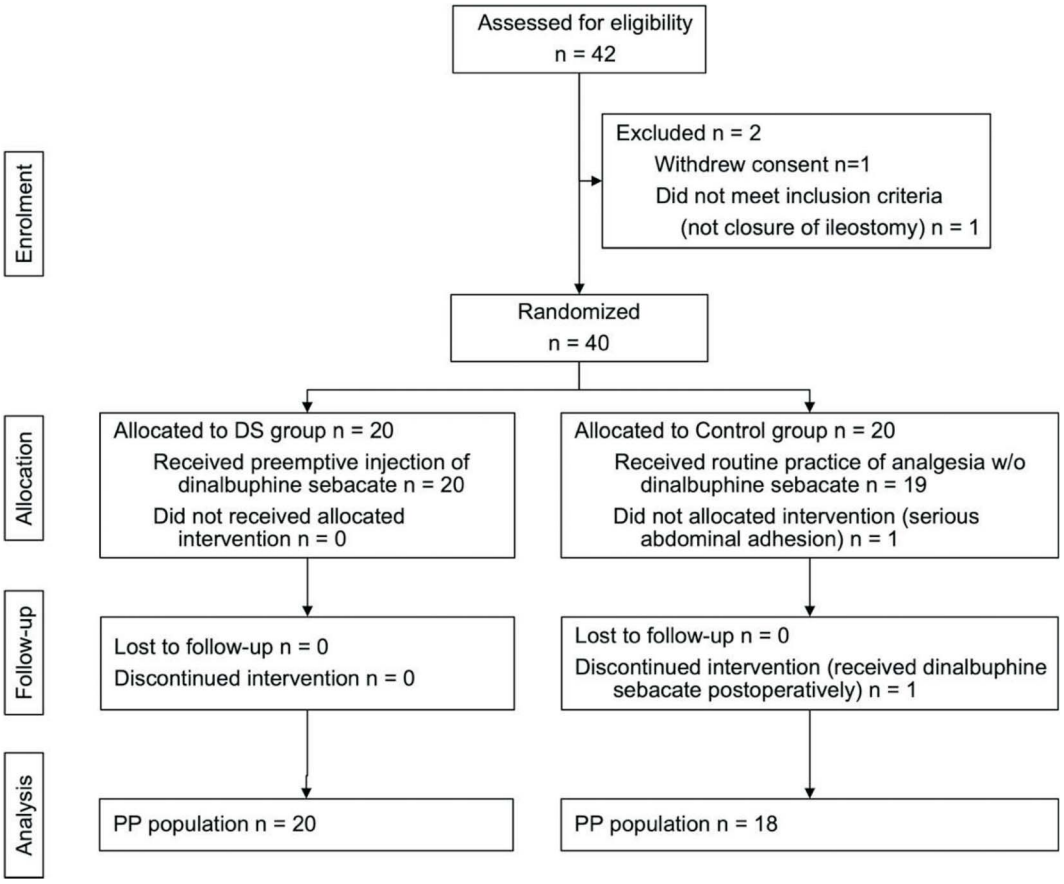

Fig. 1. Flow diagram of patient enrollment.

Table 1. Demographics and baseline information

	Dinalbuphine sebacate (n = 20)	Control (n = 18)	*p* value
Male, n (%)	16 (80.0)	14 (77.8)	> 0.999
Female, n (%)	4 (20.0)	4 (22.2)	
Age (year), mean (SD)	60.7 (9.9)	62.4 (9.9)	0.600
BMI (kg/m^2)	24.3 (2.7)	22.0 (3.5)	0.039
Weight (kg), mean (SD)	66.1 (11.8)	59.9 (12.5)	0.125
Height (cm), mean (SD)	164.4 (8.3)	164.3 (8.5)	0.971
Primary pathology and flexure, n (%)			0.929
Rectal cancer			
Upper	5 (25.0)	0 (0.0)	
Middle	9 (45.0)	9 (50.0)	
Low	5 (25.0)	7 (38.9)	
RSJ colon cancer	0 (0.0)	2 (11.1)	
Sigmoid cancer	1 (5.0)	0 (0.0)	
Stage, n (%)			0.354
I	4 (20.0)	4 (22.2)	
II	3 (15.0)	5 (27.8)	
III	5 (25.0)	2 (11.1)	
IV	5 (25.0)	5 (27.8)	
Complete remission	2 (10.0)	0 (0.0)	
Length of surgery (h), mean (SD)	1.6 (0.4)	1.6 (0.5)	> 0.999
Period from the surgery to discharge (days), mean (SD)	3.3 (1.0)	3.4 (0.8)	0.737

SD, standard deviation; BMI, body mass index.

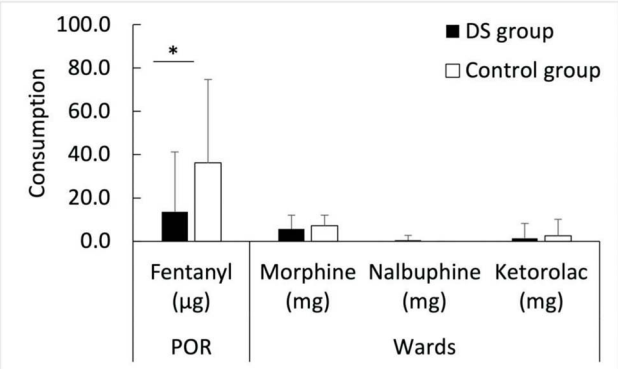

Fig. 2. Consumption of analgesics. *p* values were derived using the unpaired *t* test; * $p < 0.05$ is considered statistically significant. Dots indicate the mean value and error bars indicate the standard deviation. POR, postoperative recovery room.

fied with the postoperative pain management (data not shown).

Safety

No serious adverse reactions (ADRs) occurred in the present study (Table 3). The most frequently reported ADRs were nausea and vomiting, which are common postoperative complications associated with various surgeries. The incidence of ORAEs was 35.0% and 44% in the DS and control groups, respectively ($p = 0.741$; Table 3). Most ORAEs were mild, and only three patients required treatments (two in the DS group and one in the control group). During the follow-up

Table 2. Postoperative pain intensity

	Dinalbuphine sebacate (n = 20)	Control (n = 18)	*p* value
Surgical day, mean (SD)	3.9 (1.2)	4.9 (1.1)	0.010*
POD 1, mean (SD)	1.5 (0.9)	2.5 (1.8)	0.045*
POD 2, mean (SD)	1.2 (0.6)	1.2 (0.6)	0.767
POD 3, mean (SD)	1.2 (0.6)	1.3 (0.7)	0.613
POD 4, mean (SD)	1.2 (1.2)	1.6 (1.0)	0.314
POD 5, mean (SD)	1.1 (1.2)	1.9 (1.6)	0.105
POD 6, mean (SD)	0.8 (1.0)	1.3 (1.2)	0.205
POD 7, mean (SD)	0.6 (0.8)	1.1 (1.1)	0.128

* Statistically significant.
POD, postoperative day. SD, standard deviation.

period, one patient in the DS group experienced a serious adverse event of acute cholangitis, which was unrelated to DS. No anastomotic leakage, bowel obstruction, surgical site infection, or respiratory depression occurred.

Discussion

This prospective, open-label, randomized study demonstrated that the preoperative injection of extended-release DS significantly reduced the amount of fentanyl used in the POR and the pain intensity on the surgery day and POD 1 in patients undergoing ileostomy reversal. On POD 2, the mean pain scores were not higher than 2.0; therefore, achieving significant differences between both groups was difficult. No serious ADRs occurred in the present study, and no significant difference in ORAE incidence was noted, which indicated the safety of DS.

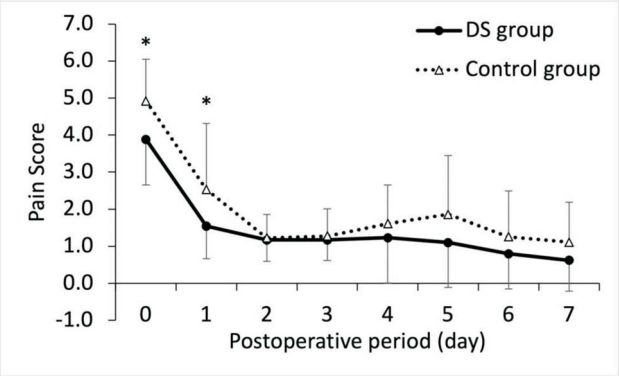

Fig. 3. Postoperative pain intensity curve. *p* values were derived using the unpaired *t* test; * $p < 0.05$ is considered statistically significant. Dots indicate the mean value and error bars indicate the standard deviation.

With the long-acting formulation and reduction of fentanyl consumption observed in the study, preoperative DS may serve as the background analgesia that escalates the pain threshold, resulting in the requirement of fewer rescue analgesics for postoperative pain management. Similarly, we noted that 10% of patients in the DS group did not require additional rescue analgesics on the first 3 days after surgery, during which patients are most likely to experience extreme postoperative pain and require rescue analgesics. The single-dose 150 mg DS provided satisfying pain management, with fewer treatments required during recovery, which may in turn decrease the medical burden.

Ileostomy reversal studies have broadly discussed postoperative complications, including anastomotic leakage, surgical site infection, morbidity, and mortality. Few studies have reported on adequate postoperative acute pain management and CPSP incidence.[22,23] Suh et al. reported moderate-to-severe pain following ileostomy reversal, which persisted NRS > 4 for 3-4 days under general analgesics treatment.[23] However, in the present study, the mean NRS scores were all less than 3 since POD 1 in both groups. Furthermore, on the surgery day, patients receiving preoperative extended-release DS experienced a remarkably reduced pain intensity (NRS < 4), which was also significantly lower than that in the control group; this control group had NRS of at least 1 point higher. All patients received appropriate pain management.

Studies have suggested that the clinically significant change in the pain intensity rated using the 11-point NRS was approximately 1.39-1.41, and that as-

Table 3. Safety information

	Dinalbuphine sebacate (n = 20)	Control (n = 18)	*p* value
Number of subjects with adverse events, n (%)	11 (55.0)	10 (55.6)	> 0.999
Number of subjects with ORAEs, n (%)	7 (35.0)	8 (44.4)	0.741
Number of subjects with adverse drug reactions, n (%)			
Nausea	6 (30.0)	4 (22.2)	0.719
Injection site reaction	3 (15.0)	0 (0.0)	0.232
Vomiting	3 (15.0)	2 (11.1)	> 0.999
Dizziness	0 (0.0)	2 (11.1)	0.218

Opioid-related adverse events (ORAEs) included nausea, vomiting, and dizziness.

sessed using the 10-cm VAS was 1 cm.[24-26] In our study, although the difference in mean NRS scores between the DS and control groups did not achieve the clinically significant change of 1.39-1.41, the preoperative extended-release DS exerted beneficial effects, producing the subjective primary outcome, namely reduction in fentanyl consumption in the POR. Both the objective and direct parameter (i.e., pain scores) and the subjective and indirect parameter (i.e., analgesic consumption) should be considered when the effects of an analgesic agent are evaluated.

No opioid antagonism or severe nalbuphine-induced adverse events occurred during the study. The single-dose, extended-release DS might result in a relatively stable blood concentration of nalbuphine compared with short-acting DS, which decreased the incidence of related adverse events.[27] Inevitably, postoperative nausea and vomiting were observed in the DS group, but no significant differences were noted between the groups. Injection site reactions (ISRs), such as swelling and erythema, are frequent adverse events associated with the oil-based formulation of injection products administered intramuscularly. Compared with the previous study,[19] the current study reported a lower incidence of ISRs, possibly because ultrasound-guided injections were administered. Ultrasound-guided injections provide a clear vision of the border between the muscle layer and lipid-rich hypodermis layer to ensure that drugs are injected into the muscle, thus preventing ISRs.[28] Whether ultrasound-guided injections could resolve ISRs caused by DS should be investigated in future studies.

Although the analgesic regimens in the current study are similar to those used in previous studies, the efficacy of DS in the early recovery period was different. A study on laparoscopic cholecystectomy reported no significant difference in the average postoperative pain intensity and opioid consumption between the DS-receiving group and control group.[29] By contrast, Chang and colleagues demonstrated that DS significantly reduced the postoperative pain intensity in patients who underwent CRC laparotomy, which causes more severe pain than laparoscopic cholecystectomy.[30] In our study, the mean pain scores were significantly low in the DS group on the surgery day and POD 1, and fentanyl consumption in the POR was also low in the DS group. However, no significant difference in the pain intensity or amounts of analgesics administered was observed after POD 1. Thus, the more severe the pain the patients experienced, the more obvious the effects of analgesics and their benefits. The surgical procedure determines the postoperative pain intensity and therefore is the most critical factor when planning the study design. Investigating DS in patients receiving surgeries that may cause more severe or persistent pain is appropriate. For minimally invasive surgeries, quality-of-life questionnaires or assessments of postoperative chronic pain may be considered.

This study has some limitations. First, the assessment of patient-reported pain intensity inherently involved a degree of subjectivity; therefore, the open-label design may have affected the difference in NRS scores between the two groups. Administering a preoperative placebo injection to the control group may minimize such bias; however, placebos packaged in same containers of approved drug were difficult to be obtained. Furthermore, in phase IV studies, the benefits of placebo injection design may not outweigh the related risks. Second, although our study successfully detected a significant difference in the primary outcome, consumption of fentanyl in POR, the sample size was too small to demonstrate the effect of DS on reduction of postoperative opioid consumption and the adverse reactions with incidence less than 1%. Lastly, the study was conducted at a single center, which raised the concern of generalizability. The results may not be applied to a large population. Future large-scale controlled trials are warranted to validate our outcomes.

Conclusions

Compared with traditional intravenous opioid drugs, the single-dose, long-acting DS administered preoperatively effectively relieved postoperative pain in patients undergoing ileostomy reversal and was well tolerated by them.

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原　著

納疼解用於造口接合手術術後止痛：一項隨機分組開放性研究

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目的　止痛是造口關閉手術術後管理的重點之一，它與患者的康復、併發症發生率和醫療滿意度密切相關。Dinalbuphine sebacate (DS) 為一新型長效止痛劑。本研究為開放性、隨機分組設計，針對 DS 應用於迴腸造口關閉手術術後止痛的有效性和安全性進行觀察分析。

材料與方法　本研究納入已接受過腹腔鏡手術並計劃進行迴腸造口關閉的患者進行研究，隨機分為 DS 組和對照組。DS 組患者在術前 12 小時於臀大肌注射一劑 2 毫升、150 mg 的 DS。兩組均在術後恢復室依患者需求給予芬太尼；在病房中，對疼痛分數 ≥ 4 或 < 4 的突發性疼痛，分別給予阿片類藥物或酮咯酸。

結果　共計 38 名患者完成所有評估項目。主要終點-平均芬太尼消耗量，在 DS 組顯著降低 (13.8 ± 27.5 μg vs. 36.1 ± 38.6 μg, $p = 0.045$)。在病房內的嗎啡、納布啡和酮咯酸使用量，兩組間沒有顯著差異。與對照組相比，DS 組術後第 0 天 (3.9 vs. 4.9, $p = 0.010$) 和第一天 (1.5 vs. 2.5, $p = 0.045$) 的疼痛強度較低。自第二天起，兩組的平均疼痛評分均低於 2.0，無顯著差異。本研究未觀察到嚴重不良反應。

結論　長效緩釋 DS 安全地減少了阿片類藥物的消耗和迴腸造口關閉手術後的疼痛強度。

關鍵詞　納疼解 (Dinalbuphine sebacate)、迴腸造口關閉手術、嗎啡、術後止痛。