

Preoperative Administration of Extended-Release Dinalbuphine Sebamate Compares with Morphine for Post-Laparoscopic Cholecystectomy Pain Management: A Randomized Study

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Sing-Ong Lee¹
Li-Ping Huang¹
Chih-Shung Wong¹⁻³

¹Department of Anesthesiology, Cathay General Hospital, Taipei, Taiwan;
²Graduate Institute of Medical Science, National Defense Medical Center, Taipei, Taiwan; ³School of Medicine, Fu-Jen Catholic University, New Taipei, Taiwan

Purpose: Perioperative pain management plays a critical role in the effort to promote enhanced recovery after surgery (ERAS). Pain is also the most concern for patients after laparoscopic cholecystectomy (LC). Naldebain (extended-release dinalbuphine sebamate, DS) is an oil-based formulation for intramuscular injection that has been designed for extended release and can be used for preoperative analgesia over a 7-day period. This study was aimed to compare the efficacy of DS injection with that of regular postoperative morphine administered when necessary for the management of post-laparoscopic cholecystectomy pain.

Patients and Methods: Forty-four patients scheduled for elective laparoscopic cholecystectomy were included in this prospective study. The patients were allocated randomly into two groups, with equal numbers receiving preoperative DS versus post-operative morphine. A total of 21 and 22 patients completed the study within the preoperative DS and post-operative morphine group, respectively.

Results: There were no statistically significant differences between two treatment groups with respect to length of surgery, anesthetics used during operation, or the average visual analog scale pain score in the post-operative anesthesia care unit (PACU), and at 4, 24, 48, and 72 hours post-procedure. Morphine was required only during the first postoperative day among those in the DS group. Safety was comparable in both DS and morphine groups.

Conclusion: A single preoperative dose of DS provides sufficient analgesia along with a manageable safety profile and no interference with surgical anesthetics when compared to control cases that underwent surgery without preoperative DS treatment. This pilot study suggests that preoperative administration of DS is safe and may decrease the need for postoperative opioid use after laparoscopic cholecystectomy.

Registration: ClinicalTrials.gov Identifier: NCT03713216.

Keywords: nalbuphine, enhanced recovery after surgery, multimodal analgesia, preventive analgesia

Introduction

Appropriate perioperative pain management is critical factor in the effort to achieve enhanced recovery after surgery (ERAS).¹ Although various analgesics had been studied for postoperative pain management, opioids remain the mainstay in most clinical settings.² Opioid administration results in numerous adverse effects, including pruritus, constipation, and respiratory depression.³ Multimodal opioid-sparing regimens have been devised to address concerns associated with high dose-opioid

Correspondence: Chih-Shung Wong
Department of Anesthesiology,
Cathay General Hospital, #280, Renai
Road, Section 4, Taipei, Taiwan
Tel +886-2-27082121 Ext 3510
Fax +886-2-87924835
Email w82556@gmail.com

use; these typically involve combinations multiple drugs to promote pain relief using different pathways and mechanisms of action and achieve more effective analgesia while limiting opioid consumption.⁴

Laparoscopic procedures are in wide use and present many advantages for the surgeon and the patient including minimized surgical complications and decreased pain intensity; these factors all contribute positively to patient recovery.^{5,6} One growing concern after laparoscopic procedure is chronic postoperative pain (CPSP) formation; this is because most of the CPSP developed when postoperative acute visceral pain persisted after discharge.⁷ In recent years, a significant effort has been made towards the identification of optimal combinations of medications for preoperative analgesia; these are widely used to facilitate postoperative outcomes following laparoscopic procedures.^{8,9} As one example, 8 mg of dexamethasone provided significantly better pain relief when administered preoperatively rather than postoperatively.¹⁰ Likewise, Wilson et al demonstrated that intramuscular diclofenac after laparoscopic cholecystectomy (LC) was effective in reducing postoperative pain.¹¹ However, there is as yet no clear understanding of the optimal timing of interventions or regarding specific multimodal regimens for analgesia for LC.¹²

Dinalbuphine sebacate (DS) injection (Naldebain ER Injection, Lumosa Therapeutics, Taiwan) was designed as a prodrug form of nalbuphine with similar analgesic effects as morphine. Intramuscular DS injection slowly releases into the blood vessel and maintain relatively low nalbuphine concentration covered early recovery period that decreases postoperative pain intensity and threshold of pain feeling. The formulation includes a sesame oil-based solution with 150 mg DS in a 2 mL volume and has been approved for moderate to severe pain relief by the Taiwan Food and Drug Administration (TFDA). Recommended administration time is at least 12 hours prior to surgery. Previous studies have revealed that preoperative administration of DS resulted in effective pain control for 7 days and was associated with a significant reduction in postoperative ketorolac consumption after hemorrhoidectomy.¹³

The postoperative analgesic effect of morphine has been studied in association with many types of laparoscopic surgery.^{14–16} Most studies focus on pain relief or the use of rescue medication in the first 24 hours after surgery. Blichfeldt-Eckhardt et al⁷ found that early visceral pain was associated with chronic pain at 12 months after LC. Likewise, Richebe et al¹⁷ noted that the

incidence of chronic pain reached 3–56% among cases in which there was no effective strategy to limit persistent postoperative pain. We recently reported combination use with ultrasound-guided peripheral nerve block, epidural anesthesia, and the extended-release DS provided additional postoperative analgesia and longer duration of time reported as pain-free after surgery.^{18,19} These studies underscore a potential role for extended-release DS as a component of perioperative multimodal analgesia.²⁰ At this time, there are limited data that propose the utility of extended-release DS for the management of acute postoperative pain in early and intermediate recovery periods in patients undergoing LC. In this study, we aimed to evaluate the effect of preoperative treatment with extended-release dinalbuphine sebacate for postoperative pain relief after elective LC compared with responses to conventional postoperative intravenous morphine treatment.

Patients and Methods

Patients

This was a prospective, randomized-controlled clinical study that was registered on ClinicalTrials.gov (Identifier: NCT03713216) prior to enrolling study participants. This study protocol was approved by the Institutional Review Board of Cathay General Hospital (CGH-P107007) and conducted in accordance with the Declaration of Helsinki. The study flow diagram is presented in [Figure 1](#). Patients were enrolled at Cathay General Hospital, Taipei from October 2018 to October 2019. Written informed consent was obtained from all patients prior to screening for enrollment. All data for background information, efficacy, and safety were collected anonymously and in compliance with the Declaration of Helsinki. Eligible patients were aged 20 years or older and scheduled for elective LC under general anesthesia. Patients meeting the following criteria were excluded from the study: those not willing to adhere to the study visit schedule; those with a history of hypersensitivity or allergy to opioids, NSAIDs or sesame oil, or any clinically significant condition that may interfere with study assessments; those who were pregnant or breastfeeding; those with a medical history that may predispose them to abnormal intracranial pressure; or any history of narcotic dependency, addiction, and withdrawal.

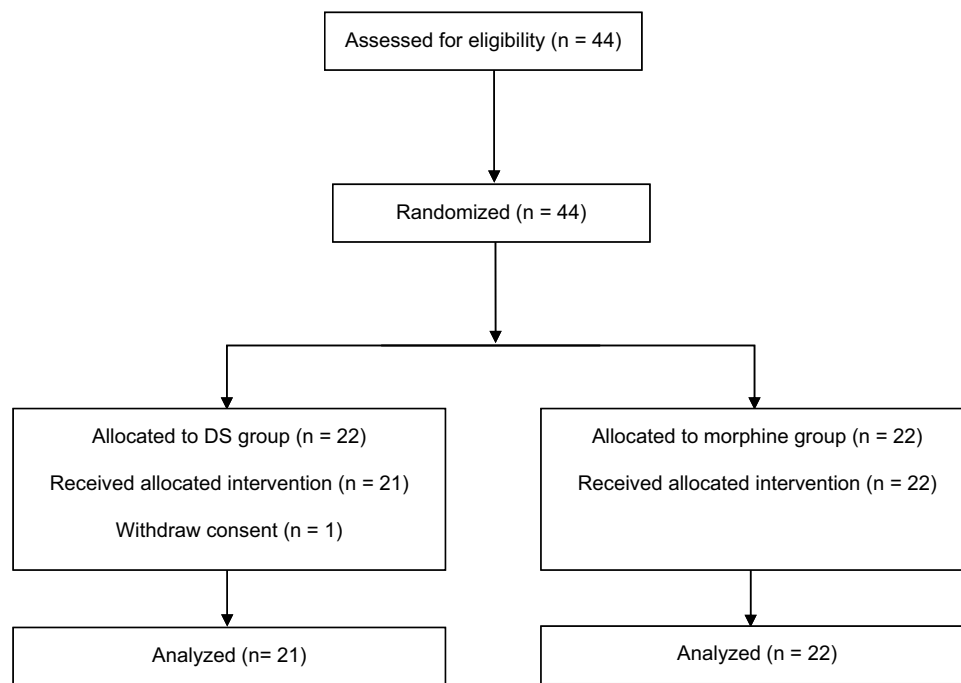


Figure 1 The consort flow diagram.

Procedure

All patients were randomly assigned (half in each group) to receive either a 150 mg DS injection (DS group) preoperatively or regular morphine after surgery (Morphine group). Random numbers and assignment treatment were generated by computer program before this study initiated. Once the patient was eligible, the random number was assigned and allocated to pre-defined treatment. Patients in the DS group received a single dose of 150 mg DS was injected intramuscularly at least 12 hours prior to surgery. Patients in the Morphine group received intravenous morphine as needed for postoperative pain. Anesthesia was induced in both treatment groups with 2 mg/kg propofol, 2 µg/kg fentanyl, 0.6–1 mg/kg rocuronium bromide; anesthesia was maintained with 1–1.2 minimum alveolar concentration (MAC) of sevoflurane and 100–300 µg fentanyl during the procedure as needed. Anesthesiologists were blinded to the patient treatment group. Either ketorolac or morphine was prescribed to patients in both groups as rescue analgesics by surgeons' orders when needed; rescue analgesics (5 mg morphine or 30 mg ketorolac per time) were recommended for patients with a VAS above 3.0. The quantity and frequency of rescue analgesics were recorded.

Patients were provided with instructions on the use of the 100-mm visual analog scale (VAS; 0 = no pain, 100 mm = the worst pain) and other assessments before the first evaluation. The VAS for pain was recorded by patients themselves in the PACU, and at 4, 24, 48 and 72 hours after surgery. Daily vital signs, any injection site reactions, concomitant medications, and adverse events were recorded by investigators starting from the time of administration of the study medications until discharge. Patients' satisfaction was evaluated at day 3 using 5-grade score (highly satisfied, satisfied, uncertain, not satisfied, highly unsatisfied).

Statistical Analysis

At least 42 patients were needed in order to detect differences in pain scores within 24 hours after LC with α level of 0.05 (two-tailed) and β level of 0.4 (power 60%). Analgesic interventions were scored using 10 mm VAS as a clinically meaningful improvement. This pilot study included 43 patients; 21 patients received 150 mg DS preoperatively and 22 patients received morphine only as needed for postoperative pain. Differences in average 72-hour VAS pain scores were the primary endpoint. The VAS and use of morphine and ketorolac were analyzed using a Mann–Whitney test. For categorical measures,

Table 2 Frequency and Dose of Rescue Analgesia

	DS (N=21)	Morphine (N=22)	P value
Number of subjects used morphine (%)	5 (23.8)	9 (40.9)	0.1448
Total consumption of morphine (mg)	37	92	
Mean morphine dose (mg), mean (SD)	1.76 (3.75)	4.18 (6.27)	
Number of subjects used ketorolac (%)	4 (19.0)	2 (9.1)	0.4121
Total consumption of ketorolac (mg)	120	60	
Mean ketorolac dose (mg), mean (SD)	5.71 (12.07)	2.73 (8.83)	

Notes: Derived from Mann Whitney test; P values < 0.05 were considered as statistically significant.

Abbreviations: DS, dinalbuphine sebacate; SD, standard deviation.

comparisons were analyzed by X^2 or Fisher's exact test. P values < 0.05 were considered as statistically significant.

Results

Study Participants

Forty-four patients were randomly assigned into one of two groups; the DS group received preoperative injection with DS (150 mg; n = 22) and the Morphine group received postoperative intravenous morphine as needed (n = 22; Figure 1). One patient in DS group withdrew from the study prior to the DS injection. Demographics and baseline characteristics are summarized in Table 1. There were no statistically significant differences between the two groups with respect to intraoperative anesthetic use.

Efficacy

With respect to total morphine consumption within 72 hours after surgery, patients in the DS group used slightly less opioid analgesics overall than did those in the Morphine group (37 vs 92 mg; Table 2), however, there were no statistically significant differences with respect to mean total morphine consumption after surgery (1.76 ± 3.75 vs 4.18 ± 6.27 , for DS vs Morphine groups, $p = 0.1448$).

Patients in the DS group received morphine or ketorolac only while in the PACU, while those in the Morphine group consumed on average 57, 20, and 15 mg morphine per patient on post-operative days 1, 2 and 3, respectively. Fewer patients in DS group used opioids after surgery (23.8 vs 40.9% in the DS vs Morphine groups, respectively). Both groups utilized ketorolac during post-operative day 1 only (5.71 ± 12.07 vs 2.73 ± 8.83 , for DS vs Morphine groups, $p = 0.4121$). Comparison of post-operative pain intensity at consecutive intervals revealed no statistically significant differences between the two groups while in the PACU, or at 4, 24, 48, and 72 hours after the procedure (Figure 2).

Safety

A total of 17 patients reported at least one adverse event during the study period, including 13 (61.9%) and 4 (18.2%) patients assigned to the DS and Morphine groups, respectively (Table 3). All adverse events were mild to moderate and required no specific drug treatment.

The most frequent adverse events were postoperative nausea and vomiting in the DS group (n = 13) and fever in the Morphine group (n = 3). Although more adverse events were reported in the DS group, nearly all were mild and

Table 1 Demographic Information and Baseline Characteristics

	DS (N = 21)	Morphine (N = 22)	P value
Gender (male/female)	9/12	10/12	0.8639
Age (year)	58.2 (12.5)	49.5 (16.1)	0.0626
Weight (kg)	63.6 (10.0)	72.3 (18.1)	0.1548
Height (cm)	163.4 (7.5)	167.2 (10.8)	0.5115
BMI (kg/m ²)	23.8 (3.4)	25.5 (4.3)	0.1298
Length of surgery (minute)	69.9 (48.0)	62.3 (27.8)	0.6337

Notes: Data are presented as mean (standard deviation); P values < 0.05 were considered as statistically significant.

Abbreviation: BMI, body mass index.

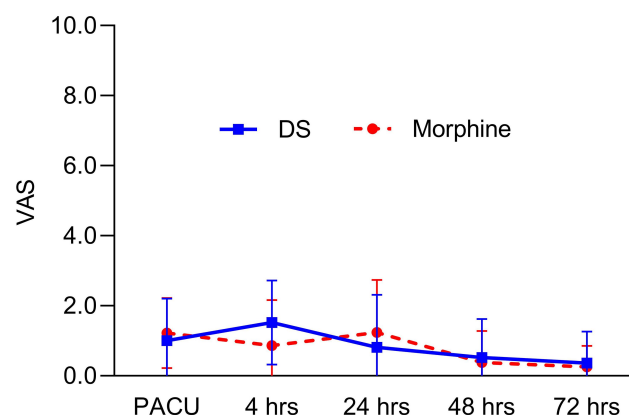
**Figure 2** Pain scores over time from PACU to 72 hours after the procedure.

Table 3 Incidence of Adverse Events During the Study Period

	DS (N=21)	Morphine (N=22)	P value
Vomiting	7 (33%)	1 (5%)	0.0212
Nausea	6 (29%)	0	0.0089
Fever	5 (24%)	3 (14%)	0.4566
Injection site reaction	2 (10%)	0	0.2326

Notes: Data are presented as n (%); Derived from Fisher's exact test.

Abbreviation: DS, dinalbuphine sebacate.

resolved by postoperative day 1. Two patients in DS group reported swelling at the injection site that resolved by days 4 and 8 after DS injection, respectively. In the Morphine group, three subjects experienced moderate fever and one subject vomited twice. Both groups expressed a high degree of satisfaction with postoperative analgesia (100% vs 95% in DS and Morphine groups, respectively).

Discussion

To the best of our knowledge, this is the first report describing the analgesic impact of preoperative extended-release DS compared with regular intravenous morphine for the management of post-LC pain. Among our findings, there were no statistically significant differences in average visual analog scale pain score when comparing those in the DS group to those treated postoperatively with intravenous morphine alone. Mean VAS score at each time-point was below 2; this result indicates that both groups received adequate postoperative pain relief. The fact that no opioids were required after 24 hours post-procedure underscores the efficacy of preoperative DS; administration of DS prior to LC resulted in no severe adverse events and was not associated with any opioid antagonism among the patients in this study.

However, our findings contradict those in a previous report in which preoperative injection of DS was associated with a superior level of pain reduction and use of fewer rescue analgesics compared to placebo in patients undergoing hemorrhoidectomy.¹³ When analyzing outcomes from these two studies, there are important differences that provide clarification. First, the magnitude of postoperative acute pain after LC was much lower (minimum to maximum range: 0.8–1.5) than that associated with hemorrhoidectomy (minimum to maximum range: 2.4–5.4) during the first day after surgery;^{17,21} as such, the absolute magnitude of pain reduction associated with DS administration was more difficult to evaluate in our study.²² Second, hemorrhoid pain is a mix of

visceral and somatic pain and typically persists for several days at the moderate to severe level. However, compared with previous studies that focus on LC, the pain profile is typically at mild intensity (VAS was less than 3) at 24 hours after surgery; as such, the impact of analgesics was not easily recognized. Finally, our study was not double-blinded; as such, it is possible that preoperative treatment with DS may promote some degree of bias based on psychological expectations.²³ Interestingly, Riest et al²⁴ found that preoperative analgesia with a single dose of the cyclooxygenase inhibitor, parecoxib, did not lead to universally positive effects on pain score or on the total amount of rescue medication required when compared to use of postoperative analgesia alone.

There were several limitations to our study. First, we did not include a placebo control which would have permitted us to compare our findings to those reported previously. Moreover, patients with gallstones or cholecystitis were eligible for enrollment in this study; as such, tissue inflammation or infection prior to surgery might have an impact on valid postoperative pain and increase incidence of postoperative fever.²⁵ In addition, in accordance with our standard of care, all patients in this study received antiemetics as needed, although this was not mandatory before surgery; as such, it is possible that was associated with the increased incidence of nausea and vomiting in DS group. From our study, we recommend routine administration of antiemetics to be given with preoperative DS treatments.

Due to the fact that nalbuphine is a kappa-receptor agonist and mu-receptor antagonist, it has the potential to increase the risk of opioid-antagonism; this could result in the need for an increased anesthetic dose and/or more severe adverse events. However, our results revealed no significant differences in anesthetic consumption during the procedure. Indeed, more postoperative nausea and vomiting were observed among patients in DS group; these events were mild and resolved in a few hours after appropriate treatment with antiemetics. Most of the rescue morphine used among those in the DS group was for abdominal pain associated with carbon dioxide retention while in the PACU. Carbon dioxide retention in the abdomen, which is typically trapped between liver and right diaphragm, was reported to be a significant cause of abdominal pain and referred shoulder pain.^{26–28} It is possible that this factor contributes to the consumption of more opioid analgesics at day 1, although this was not observed in the previous hemorrhoidectomy study.

One study has reported that administration of low concentrations of nalbuphine may result in diminished levels of opioid-related side effects, such as pruritus.²⁹ Our

results showed that the two treatments had a similar safety profile; none of the patients treated with DS reported postoperative pruritus, even among those who received rescue morphine. Based on pharmacokinetics of DS, the relatively low concentration of nalbuphine provided a background analgesic effect³⁰ which might explain why patients in DS group required no supplemental analgesics after 24 hours, by contrast those in the postoperative morphine group.

Conclusion

This study demonstrated that patients receiving preoperative treatment with DS consumed less opioid analgesic after 24 hours with similar satisfactory levels of post-LC pain relief.

Data Sharing Statement

The data collected or analyzed in this study will be available 6 months after publication. Anyone who wishes to access those data could contact the corresponding author by email.

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Disclosure

The authors report no conflicts of interest in this work.

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