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Effect of Dinalbuphine sebacate on postoperative multimodal analgesic strategy in video-assisted thoracoscopic surgery: a double-blind randomized controlled trial

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Abstract

Background Multimodal analgesia (MMA) combines different analgesic methods, such as non-steroidal inflammatory drugs (NSAIDs), acetaminophen, and regional anesthesia techniques, to optimize pain control while minimizing opioid use. Dinalbuphine sebacate (DS), a long-acting prodrug of nalbuphine, was chosen due to its potential to enhance MMA strategies. The aim of this study is to evaluate the effectiveness of DS in MMA for video-assisted thoracoscopic surgery (VATS).

Methods Sixty participants were randomly and equally assigned to either the MMA regimen containing DS (DS group) or placebo (placebo group). After anesthesia induction, all participants received ultrasound-guided thoracic paravertebral block (TPVB), and DS or placebo was injected into the gluteus medius muscle on the operated side. Intravenous patient-controlled analgesia (IVPCA) with fentanyl was provided for breakthrough pain postoperatively. The primary outcome was postoperative fentanyl consumption over three days. Statistical tests included Student's *t*-test, chi-square test, and Fisher's exact test.

Results Finally, 57 participants were assigned to either the DS group ($n=28$) or the placebo group ($n=29$). The mean fentanyl consumption over three days was significantly lower in the DS group (283 ± 70 μg) compared to the placebo group (708 ± 190 μg, $P<0.001$). Pain interference with daily life was significantly lower in the DS group at one week (28.57% vs. 86.2%, $P<0.001$) and one month postoperatively (10.71% vs. 48.28%, $P=0.003$). Pain intensity during movement was significantly lower in the DS group at one week (2.07 ± 0.61 vs. 4.00 ± 0.56, $P<0.001$) and one month (0.64 ± 0.35 vs. 2.10 ± 0.4, $P<0.001$).

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Conclusions By providing superior analgesia, reducing opioid requirements, improving functional recovery and its long-lasting effect after discharge, DS enhanced postoperative MMA for VATS.

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Keywords Dinalbuphine, Nalbuphine, Video-assisted thoracic surgery, Fentanyl, Multimodal analgesia

Introduction

Video-assisted thoracoscopic surgery (VATS) has become a popular technique for lung cancer resection due to its ability to reduce surgical stress and postoperative pain compared with conventional thoracic surgery. However, patients undergoing VATS may still experience moderate to severe pain immediately after the procedure, with a reported prevalence of 15.7% within 48 h [1, 2]. In some cases, if acute severe postoperative pain is not adequately managed, it may progress to chronic post-surgical pain (CPSP), which lasts for more than three months. Studies have shown that even after excluding other causes of pain, such as infection or recurring malignancy, the incidence of CPSP after VATS ranges from 20 to 47% [3, 4]. Various pain management regimens, often combining non-steroidal anti-inflammatory drugs (NSAIDs) and opioids, have been documented in the literature for managing postoperative pain after VATS [5, 6]. Despite efforts to implement opioid-sparing pain management strategies, opioids were still necessary through patient-controlled analgesia (PCA) system to provide adequate pain relief when needed [7].

Acting as a moderate-efficacy partial agonist or antagonist of the μ-opioid receptor and as a high-efficacy partial agonist of the κ-opioid receptor, nalbuphine offered relief from moderate to severe pain without causing euphoria or respiratory depression [8–10]. Dinalbuphine sebacate (DS) injection (Naldebain® ER Injection, Lumosa Therapeutics, Taiwan), a long-acting nalbuphine, has been developed as a potential solution for proplonged analgesia. This formulation includes a sesame seed oil-based solution containing 150 mg DS in a 2 mL volume and has been approved for pain relief by the Taiwan Food and Drug Administration. Intramuscular injection of DS has been shown to provide extended analgesic effects and significantly reduce pain intensity up to 7 days after hemorrhoidectomy [11].

Thoracic paravertebral block (TPVB) is the first choice of regional analgesic technique used for VATS, as it administers local anesthetics near the thoracic vertebrae where spinal nerves emerge [12]. TPVB has demonstrated effective pain relief in several studies when incorporated into a multimodal analgesia (MMA) protocol for VATS [13, 14], although the combination of DS with TPVB has not yet been investigated. Accordingly, this study aimed to evaluate the effectiveness of TPVB combined with non-controlled DS as part of an MMA protocol for perioperative pain management following VATS. The primary endpoint was the amount of supplemental fentanyl administered during the postoperative period. Secondary endpoints included numerical rating scale (NRS) pain intensity scores over three days following surgery; pain assessments at one week and one month postoperatively; and patient satisfaction. Safety assessment included the patient's level of consciousness in the recovery room, as well as the incidence and severity of complications such as postoperative nausea and vomiting (PONV), fever, dizziness, and injection site reaction.

Methods

Ethics

Ethical approval for this single-center, prospective randomized controlled trial (IRB number KMUHIRB-F(I)-20210087, approved on 07/05/2021) was granted by the Institutional Review Board of Kaohsiung Medical University Chung-Ho Memorial Hospital, Kaohsiung, Taiwan (Chairman: Hsueh-Wei Yen, MD, PhD). The study was also registered on ClinicalTrials.gov (NCT04962152; Date: 14/07/2021). Participants were enrolled from July 15,2021, to October 2022 at Kaohsiung Medical University Chung-Ho Memorial Hospital. Written informed consent was obtained from all participants prior to enrollment.

Participants

The inclusion criteria for this study were as follows: (1) age between 20 and 65 years; (2) American Society of Anesthesiologists (ASA) physical status classification from I to III; and (3) scheduled to undergo VATS under general anesthesia. The exclusion criteria included: (1) patients with a communication disorder; (2) patients with coagulopathy, severe hepatic or renal impairment, active infection, or uncontrolled diabetes or hypertension; (3) patients with a body mass index (BMI) less than 18.5 or greater than 35.0; (4) pregnant or breastfeeding patients; (5) patients who had taken opioids for more than three weeks prior to surgery; (6) contraindications to local anesthesia; (7) patients with a history of chronic pain; and (8) patients with a history of drug allergy to DS (drug being studied), opioids, non-steroidal anti-inflammatory drugs (NSAIDs), or sesame seed oil.

General anesthesia technique

Routine monitoring, including pulse oximetry, noninvasive blood pressure, and 3-lead ECG, was established in the operating room After pre-oxygenation, anesthesia was induced with intravenous fentanyl (2 μg/kg), 2% xylocaine (1-1.5 mg/kg), and propofol (2 mg/kg). Intubation with a left-sided double-lumen endotracheal tube (DLT) (Broncho-Cath®; Mallinckrodt, St. Louis, MO) was facilitated with intravenous rocuronium (0.6 ~ 1.0 mg/kg) and a GlideScope® video laryngoscope (GVL; Verathon, Bothell, WA) [15]. DLT sizes used were 37 Fr. for men and 35 Fr. for women. Successful intubation was confirmed by three complete respiratory cycles detected by capnography and bilateral chest auscultation, while proper bronchial placement was verified using a flexible bronchoscope. Immediately after anesthesia induction, patients received 5 mg of intravenous dexamethasone to prevent PONV [16].

Maintenance of general anesthesia with sevoflurane and a continuous rocuronium infusion was conducted to maintain vital signs within the normal range and achieve a bispectral index (BIS) between 40 and 60. Intravenous metoclopramide (10 mg) was administered on the first postoperative day, and oral Primperan® (metoclopramide HCl, 5 mg) was given every 8 h in the ward as needed.

Pain management

All patients were randomly assigned 1:1 into one of two treatment groups: the DS Group (intramuscular DS injection) or the Placebo Group (intramuscular sesame seed oil injection). Randomization was performed using computer-generated codes sealed in opaque envelopes. Patients and anesthesiologists who collected the postoperative data were blinded to the randomized allocation. The trial was monitored for patient safety and data integrity by the Institutional Review Board. Following induction, all patients were placed in the lateral decubitus position and underwent ultrasound-guided TPVB with 20 mL of 0.5% ropivacaine at the T6 level. Fentanyl-based intravenous patient-controlled analgesia (PCA) was administered to calculate the amount of fentanyl consumed within three days after surgery. The PCA fentanyl included: (1) loading dose: 1 μg/kg; (2) bolus dose: 0.3 μg/kg; (3) lockout time: 7 min; and (4) four-hour limits: 3 μg/kg. All patients received a loading dose of PCA at the end of surgery and no additional opioids during the procedure. In the DS group, 150 mg of DS was injected into the gluteus medius muscle on the operated side under ultrasound guidance immediately after the anesthesia induction. 2 mL of sesame oil was injected in the same manner in the Placebo group. Both DS and sesame oil (placebo) were administered as intramuscular injections of identical volumes (2 mL) and appearance. Additionally, all patients received 40 mg of parecoxib intravenously before the end of surgery and again on the morning after surgery.

At ward, oral Ultracet® (Tramadol 37.5 mg & Acetaminophen 325 mg) and Cataflam® (diclofenac potassium) 25 mg were administered three times a day until discharge. The Ultracet® dose was reduced if the patient experienced side effects, such as dizziness, nausea or vomiting. After discharge from the hospital, oral acetaminophen 500 mg was administered three times a day for one week.

Outcome measurement

Demographic data including age, sex, height, weight, body mass index (BMI) and ASA classification, were recorded. Operative data, such as the type of VATS procedure, surgical time and anesthesia duration, were also documented.

The primary outcome measured was the total fentanyl consumption over the three days following surgery. Additionally, the frequency of PCA button press, both successful and unsuccessful (PCA device: CADD®-Solis Pain Management System, Smith Medical, ICU Medical, Minneapolis, State of Minnesota, USA) was recorded. The time points for data collection included: 60 min in the recovery room, the morning and afternoon of postoperative day 1, the morning and afternoon of postoperative day 2, and postoperative day 3 when the PCA device was removed.

The secondary outcome was pain intensity measured using a numerical rating scale (NRS) at rest and during movement, where 0 representing “no pain at all” and 10 represented “the worst pain ever possible” [17]. Pain intensity, postoperative dizziness, PONV, and body temperature were assessed concurrently with the primary outcome. Dizziness was evaluated using a four-grade scale (I = no dizziness or imbalance, II = occasional and mild dizziness or imbalance, III = persistent or moderate vertigo or imbalance, and IV = persistent and severe dizziness or imbalance, disturbing daily life) [18]. PONV severity was assessed using a four-grade scale (0 = no symptoms, 1 = mild, 2 = moderate, and 3 = severe). The level of consciousness in the recovery room was assessed using the Ramsay sedation scale [19]. Finally, upon withdrawal the PCA device, patient satisfaction with acute postoperative pain management was evaluated using a five-point scale (1 = very dissatisfied, 2 = dissatisfied, 3 = no opinion, 4 = satisfied, and 5 = very satisfied).

The buttock injection site was assessed at four time points: pre-surgery, post-surgery day 1, post-surgery day 2, and post-surgery day 3. The injection site was evaluated using a self-developed five-point scale (0 = no reaction; 1 = burning/stinging or pain at the injection site, but no swelling or erythema; 2 = erythema at the injection site but no swelling; 3 = erythema at the injection site and

swelling, but no treatment required; and 4 = erythema and swelling at the injection site and treatment required). These assessments were conducted and recorded by two groups of nursing staff who were blinded to the group allocation.

For long-term follow-up of postoperative pain, patients were interviewed by telephone at one week and one month after surgery. They were asked the following three questions: (1) Are you currently experiencing pain associated with this surgery? (2) Does the current pain interfere with your daily life? (3) What is your current NRS score at rest and during movement? The telephone interviews were conducted and recorded by nursing staff who were also blinded to group allocation. We ensured that postoperative pain assessment was carried out by clinical staff members different from those administering the interventions, and they too were unaware of the treatment assignments to ensure unbiased pain evaluation.

Sample size calculation

The sample size was determined based on the assumption that DS would reduce fentanyl consumption by at least 30% compared to the placebo group, with $\alpha = 0.05$ and power = 0.8. The minimum number of patients required in each group was calculated to be 24, and to account for possible dropouts, the size of each group was increased to 30, resulting in a total of 60 participants. Finally, 57 participants completed the study and were included in the analysis.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 25 software package for MAC (SPSS Incorporated, Chicago, Illinois, USA). Prior to between-group comparisons, the normality of the data was assessed using the Kolmogorov–Smirnov test. As the pain score data followed a normal distribution, the Student's *t*-test, chi-square test, and Fisher's exact test were used for comparisons. Data are presented as mean ± standard deviation or as number and percentage, as appropriate.

Results

Sixty-four patients were screened for enrollment in the study. After excluding four patients (one with chronic opioid use, one with NSAIDs allergy, and two with BMI ≥ 35 kg/m^2), 60 patients were included in the randomization process. Following randomization, three patients were excluded due to a revision of surgical technique to open thoracotomy, finally, 57 patients completed the study (Fig. 1). The clinical and demographic characteristics of each group are summarized in Table 1, and no statistically significant differences were observed between the two groups.

Intramuscular DS significantly decreased intravenous Fentanyl consumption

There was no statistically significant difference in postoperative fentanyl consumption between the two groups in the recovery room. However, the DS group consumed less fentanyl than the Placebo group on the morning of the first postoperative day (173.2 ± 48.5 μg vs. 324.4 ± 77.7 μg, $p = 0.0015$, Fig. 2A); From that point onward, the Placebo group consistently used more fentanyl at all subsequent time points. By the third postoperative day, total fentanyl consumption was significantly lower in the DS group compared to the Placebo group (283.3 ± 70.4 μg vs. 708.3 ± 190.1 μg, $p < 0.001$, Fig. 2A). Although both groups consumed a similar amount of fentanyl in the recovery room, daily fentanyl use in the Placebo group significantly exceeded that of the DS group thereafter.

Intramuscular DS significantly decreased frequency to press button of PCA and decreased scores of postoperative pain intensity

The Placebo group had a higher average cumulative button-press count than the DS group at all time points (Fig. 2B). Additionally, the Placebo group required more button presses to successfully deliver fentanyl via the PCA device, except in the recovery room (2.2 ± 0.7 vs. 1.4 ± 0, $p = 0.061$, Fig. 2B). Regarding postoperative resting pain intensity scores, the DS Group showed significantly lower scores on the afternoon of postoperative day 2 (Fig. 3A). No statistically significant differences were observed at other time points. However, for movement-related pain intensity, the Placebo group reported significantly higher scores on the afternoon of both postoperative day 1 (3.2 ± 0.4, 2.5 ± 0.4, $p = 0.033$, Fig. 3B) and day 2 (2.5 ± 0.5 vs. 1.8 ± 0.4, $p = 0.023$, Fig. 3B). Additionally, patients satisfactory scores regarding acute postoperative pain control were comparable between the groups.

Intramuscular DS significantly decreased postoperative pain after discharge from hospital

After discharge, patients were followed up via telephone interview at one-week and one-month intervals postoperatively. In terms of whether there was any pain related to this operation, the Placebo Group reported more postoperative wound pain than the DS Group at one-month (89.7% vs. 21.4%, $p < 0.001$) (Table 2). Regarding pain interference with daily activities after discharge, fewer patients in the DS group reported limitations compared to the Placebo group, both at one-week (28.6% vs. 86.2%, $p < 0.001$) and one-month follow-up (10.7% vs. 48.3%, $p = 0.003$) (Table 2). When comparing pain intensity between the groups after discharge, the Placebo group reported significantly higher resting pain one week

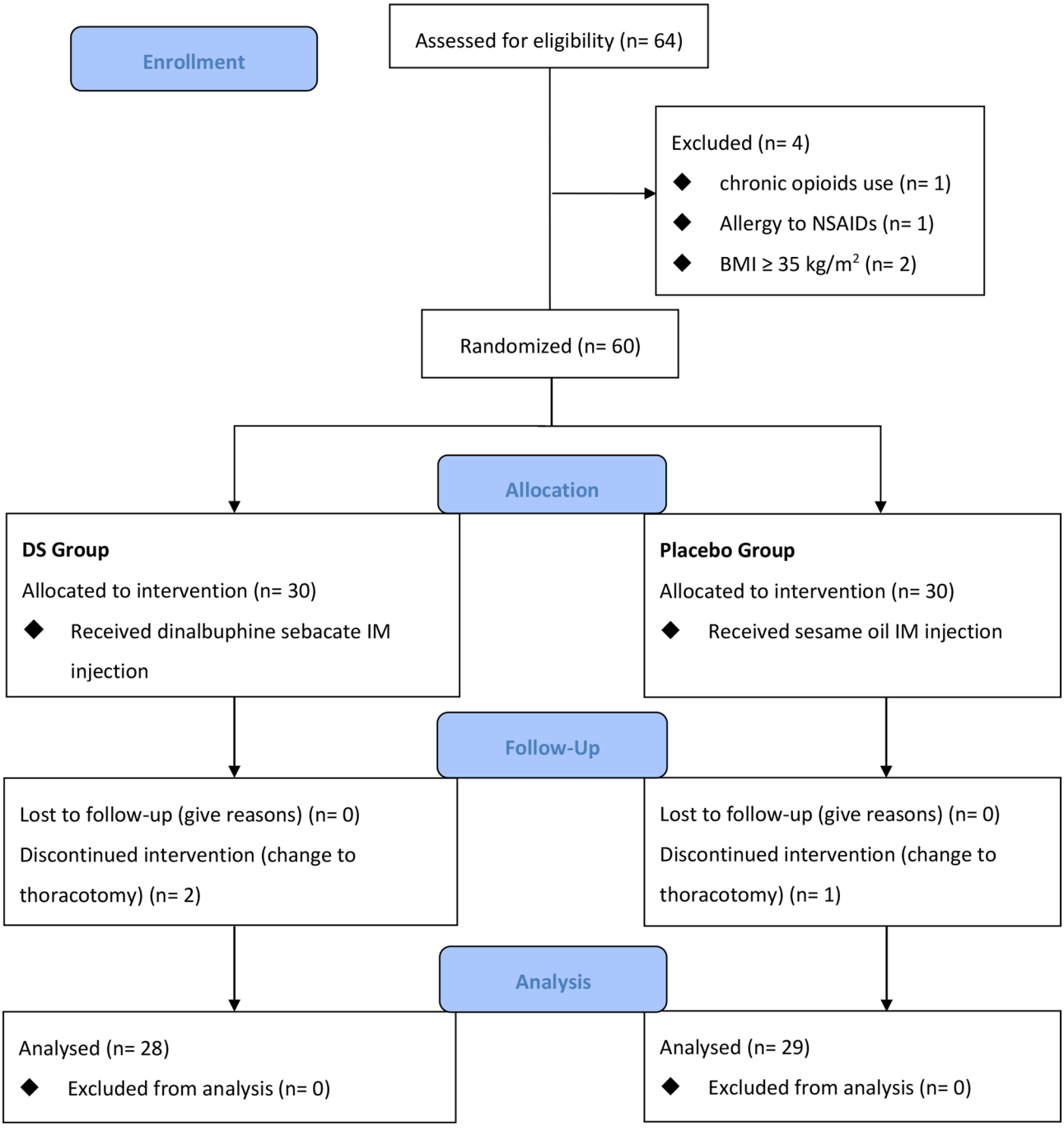

Fig. 1 CONSORT flow chart. DS, Dinalbuphine Sebacate, IM, intramuscular

postoperatively (NRS: 1.7 ± 0.5 vs. 0.4 ± 0.3, $p < 0.001$, Table 2). Additionally, movement-related pain intensity scores were significantly lower in the DS group compared to the Placebo group at both one-week (2.1 ± 0.6 vs. 4.0 ± 0.6, $p < 0.001$), and one-month (0.6 ± 0.4 vs. 2.1 ± 0.4, $p < 0.001$) respectively (Table 2).

Intramuscular DS increased incidence of mild dizziness but comparable measurements in PONV, localized injection reaction, and consciousness level

Compared with the Placebo group, the DS group showed a higher incidence of dizziness at the assessed time period of POD1-PM and POD3-AM respectively (Table 3). Although all cases involved only mild dizziness, no patients reported persistent discomfort in subsequent assessments. There were no significant differences

Table 1 Baseline characteristics of participants received MMA with placebo or Dinalbuphine Sebacate (DS) intramuscular injection for VATS

	Placebo ($n=29$)	DS ($N=28$)	*p* value
Gender: M/F	10/19	10/18	1
Age (y/o)	52.8 ± 3.4	56.7 ± 2.7	0.071
Height (cm)	161.8 ± 3.4	161.7 ± 3.2	0.96
Weight (kg)	62.8 ± 4.9	62.8 ± 5.1	0.99
BMI (kg/m^2)	23.8 ± 1.	23.9 ± 1.6	0.9
ASA: I/II/III/IV	0/24/5/0	0/22/6/0	0.747
VATS Surgical Type			
- Lobectomy	7 (24.1)	4 (14.3)	0.155
- Segmentectomy	7 (24.1)	3 (10.7)	
- Wedge Resection	12 (41.5)	20 (71.4)	
- Others	3 (10.3)	1 (3.6)	
Surgical time (min)	149.5 ± 16.6	126.9 ± 21.6	0.094
Anesthesia time (min)	199.1 ± 18.5	171.8 ± 23.4	0.066

Data are presented as mean ± SD or number (proportion). MMA, multimodal analgesia; VATS, video-assisted thoracoscopic surgery; ASA, American Society of Anesthesiologists Classification. BMI

between groups in the incidence of postoperative nausea and vomiting, consciousness level and maintenance of body temperatures above 36 degrees Celsius, all of which showed comparable outcomes (Table 4). Regarding localized buttock discomfort at injection site, one patient in the DS group at POD1 and one patient in the Placebo group at POD2 reported mild pain. However, no cases of localized swelling were observed in either group.

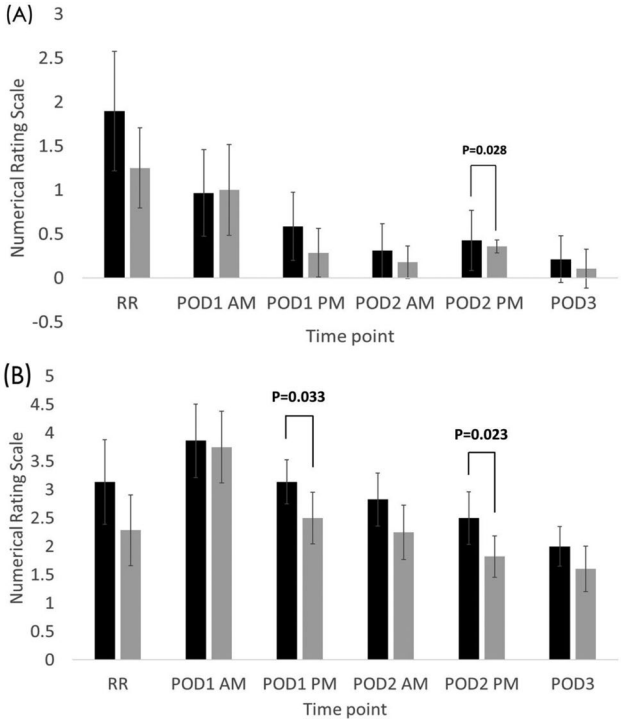

Fig. 3 Postoperative numerical rating scale pain scores (**A**) at rest and (**B**) during activity for 3 days postoperatively. Data are presented as medians with error bars showing the interquartile range. DS (gray), placebo (black). DS, dinalbuphine sebacate; RR, recovery room; POD, postoperative day; AM, Ante Meridiem; PM, Post Meridiem

Discussion

This study reported the successful implementation of a MMA protocol incorporating extended-release DS for

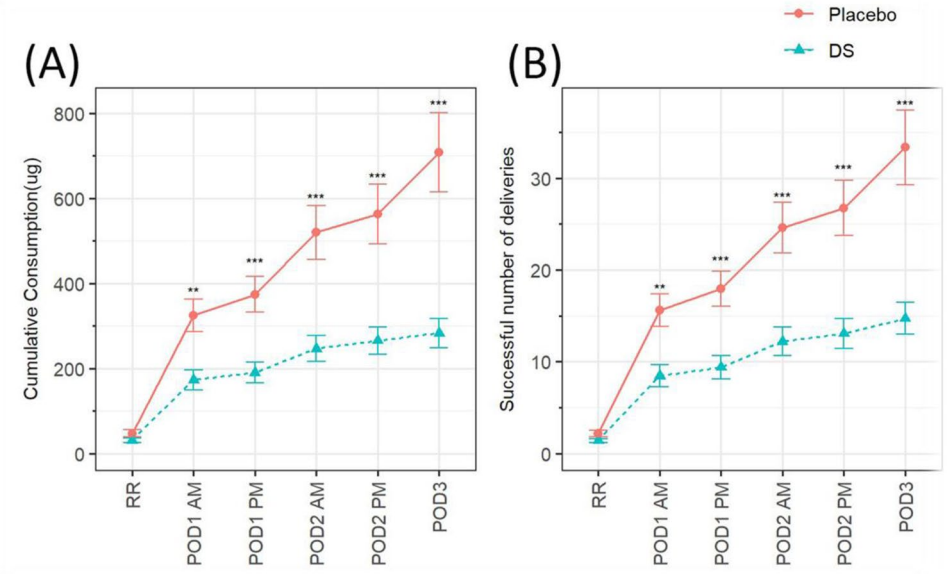

Fig. 2 Use of PCA after surgery within the first 3 days after VATS. (**A**) Cumulative consumption of fentanyl. (**B**) Successful number of deliveries. Data are presented as medians with error bars showing the interquartile range. DS (green), placebo (orange). DS, dinalbuphine sebacate; RR, recovery room; POD, postoperative day; AM, Ante Meridiem; PM, Post Meridiem; **: $p < 0.01$; ***: $p < 0.001$

Table 2 Response to the postoperative pain after discharge

	Placebo ($n=29$)	DS ($n=28$)	*p* value
Were you currently experiencing pain associated with this surgery?			
- POW1 (yes/no)	28/1 (97)	24/4 (86)	0.1936
- POM1 (yes/no)	26/3 (90)	6/22 (21)	< 0.001
Did the current pain interfere with your daily life?			
- POW1 (yes/no)	25/4 (86)	8/20 (29)	< 0.001
- POM1 (yes/no)	14/15 (48)	3/25 (11)	0.003
Pain intensity at rest (NRS)			
- POW1	1.7 ± 0.5	0.4 ± 0.3	< 0.001
- POM1	0.3 ± 0.2	0.1 ± 0.1	0.07
Pain intensity with movement (NRS)			
- POW1	4.0 ± 0.6	2.1 ± 0.6	< 0.001
- POM1	2.1 ± 0.4	0.6 ± 0.4	< 0.001

Data are presented as mean ± SD or number (proportion). DS, Dinalbuphine Sebacate; POW, postoperative week; POM, postoperative month; NRS, numerical rating scale

Table 3 Incidence and severity of postoperative nausea and vomiting (PONV)

	Placebo ($n=29$)	DS ($n=28$)	*p* value
Severity (0/1/2/3)			
RR	28/1/0/0	22/6/0/0	0.051
POD1 AM	23/5/1/0	22/3/3/0	0.561
POD1 PM	27/1/1/0	21/6/1/0	0.077
POD2 AM	28/1/0/0	24/3/1/0	0.225
POD2 PM	28/1/0/0	25/3/0/0	0.353
POD3	28/1/0/0	26/2/0/0	0.612
Incidence			
RR	1/29 (4)	6/28 (21)	0.052
POD1 AM	6/29 (21)	6/28 (21)	1
POD1 PM	2/29 (7)	7/28 (25)	0.079
POD2 AM	1/29 (4)	4/28 (14)	0.193
POD2 PM	1/29 (4)	3/28 (11)	0.353
POD3	1/29 (4)	2/28 (7)	0.612

Data are presented as numbers (proportions). DS, Dinalbuphine Sebacate; RR, recovery room; POD, postoperative day; AM, ante meridiem; PM, post meridiem; PONV severity:0, no symptoms, 1, mild; 2, moderate; and 3, severe

perioperative pain management following VATS. Currently, COX-2 inhibitors are commonly recommended as part of MMA strategy after thoracic surgery, while IVPCA is used as a rescue therapy for severe postoperative pain and allows for accurate monitoring of fentanyl consumption over the first three days. Our findings demonstrated that the addition of intramuscular DS to a postoperative MMA regimen significantly reduced the need for intravenous fentanyl during the first three days postsurgery, except during the immediate recovery room period. Intramuscular DS provided sustained postoperative analgesia, reducing moving pain in the afternoon of the first day and enhancing relief from both resting and moving pain over the following two days. After discharge, intramuscular DS consistently decreased moving pain intensity and reduced the experience of surgery-induced

Table 4 Incidence and grade of postoperative dizziness

	Placebo ($n=29$)	DS ($n=28$)	*p* value
Grade (I/II/III/IV)			
RR	19/9/1/0	14/14/0/0	0.182
POD1 AM	17/11/1/0	11/17/0/0	0.145
POD1 PM	26/1/2/0	18/9/1/0	0.009
POD2 AM	27/2/0/0	21/6/1/0	0.093
POD2 PM	26/3/0/0	22/6/0/0	0.297
POD3 AM	29/0/0/0	22/6/0/0	0.010
Incidence			
RR	10/29 (35)	14/28 (50)	0.289
POD1 AM	12/29(41)	17/28 (61)	0.189
POD1 PM	3/29 (10)	10/28 (36)	0.030
POD2 AM	2/29 (7)	7/28 (25)	0.079
POD2 PM	3/29 (10)	6/28 (21)	0.297
POD3 AM	0/29(0%)	6/28 (21)	0.010

Data are presented as Roman numerals or numbers (proportions). DS, Dinalbuphine Sebacate; RR, recovery room; POD, postoperative day; AM, ante meridiem; PM, post meridiem; Grade of dizziness: I = no dizziness or imbalance, II = occasional and mild dizziness or imbalance, III = persistent or moderate vertigo or imbalance, and IV = persistent and severe dizziness or imbalance disturbing daily life

pain and interference with daily activities. However, patients in the DS group experienced an increased incidence of dizziness on the afternoons of POD1 and POD3. Although most cases were mild, precautions should be taken to reduce the risk of falls. The incidences of PONV and localized pain at the injection site was comparable between the groups.

To administer intramuscular DS, the recommended approach is one day before surgery to obtain the optimal analgesic effect [20]; however, to prevent unnecessary fear of needle puncture and adverse events, we designed the study to administer DS to patients after the induction of anesthesia but before the surgical incision. In our MMA protocol, immediate postoperative pain control was achieved using TPVB, intravenous fentanyl, and the COX-2 inhibitor parecoxib. This approach allowed nalbuphine plasma concentrations to reach therapeutic levels on the day of surgery and through the first postoperative day. Each analgesic medication had a role in explaining why both groups had similar fentanyl consumption and pain intensity in the immediate postoperative period in the recovery room. However, as the extended-release DS gradually took effect, the DS group demonstrated fewer cumulative patient-controlled analgesia (PCA) button presses and successful deliveries, as well as significantly lower fentanyl consumption, from the morning of postoperative day one through day three, compared to the Placebo group. Although the number of successful fentanyl PCA deliveries (Fig. 2B) may not provide additional information beyond fentanyl consumption data, we believe that monitoring PCA usage (specifically, button-press attempts) provides additional insight into patients'

perceived need for analgesia, which is distinct from actual fentanyl consumption.

The major analgesic role of TPVB in the initial few postoperative hours resulted in no significant difference in pain intensity scores between the two groups in the recovery room and on the morning of POD1. However, as the analgesic effect of the nerve blockade diminished, fentanyl consumption increased, and this phenomenon indicated that the Placebo group consumed more fentanyl while still reporting higher moving pain scores in the afternoon on POD1 and POD2. Since nalbuphine is a partial antagonist of the morphine mu receptor [21], intramuscular DS presented its analgesic effects by the following morning or possibly even earlier. Previous studies have shown that combining nalbuphine with other opioids can reduce the side effects of opioids without diminishing their analgesic effect [3, 22]. In our study, we demonstrated that a combination of intramuscular extended-release DS and intravenous fentanyl produced superior analgesic outcomes compared to intravenous PCA fentanyl alone in the first few postoperative days following VATS.

Patients undergoing VATS are prone to chronic pain, with the incidence of persistent postsurgical pain originating from the surgical area ranging from 11 to 35%. Additionally, 30% of the patients reported pain-related functional impairment in daily activities [23]. Inadequate postoperative pain control after discharge has detrimental effects on quality of life and leads to the development of chronic postsurgical pain; accordingly, our research evaluated not only the acute postsurgical pain in the hospital but the pain experienced after discharge as well. The incidence of postsurgical pain in the DS Group at postoperative one month (POM1) was lower than that in the Placebo Group; moreover, at both postoperative one-week (POW1) and POM1 time points, the DS Group reported lower scores for both resting and moving pain as well as less interference with daily activities, compared to the Placebo Group. Although incisional wounds in VATS are smaller than those in conventional thoracotomy, intercostal nerve injuries remain a major cause of neuropathic pain [24]. Nalbuphine has been shown to relieve both neuropathic [25] and visceral pain [26], and with adequate acute pain relief being essential for reducing the risk of chronic pain [27], extended-release DS, with its seven-day duration of action, may play a role in suppressing both peripheral and central neuroplasticity. However, the exact underlying mechanism requires further investigation.

In the current study, only two patients (one from the DS Group and one from the Placebo group) experienced localized pain at the injection site. The incidence of DS injection-induced localized tissue pain was significantly lower than that reported in previous studies (average: 27.5%) [11, 28, 29]. This lower incidence may be attributed to the ultrasound-guided DS injection, which ensured accurate intramuscular injection, particularly into skeletal muscle, which is poorly innervated by pain fibers [30]. Furthermore, the administration of parecoxib, a COX2 inhibitor included in our MMA protocol before surgery, likely contributed to reduced postsurgical pain and inflammation, resulting in fewer and milder injection site reactions among our patients.

Postoperative orthostatic intolerance (OI), characterized by symptoms such as dizziness, nausea and vomiting, feeling hot, blurred vision, and potentially syncope, has been reported to have a high incidence of up to 35.2% after VATS [31]. The routine administration of prophylactic antiemetics (dexamethasone and metoclopramide) to prevent PONV may explain why no difference in PONV incidence was observed between the two groups. However, the occurrence of postoperative dizziness and PONV is influenced not only by the surgical procedures [32] but also by the intramuscular plasma levels of DS, which increase gradually and peak at 24–72 h post-injection [33]. Patients who received DS injections experienced dizziness during this peak absorption period.

Our study has several limitations. First, recording of consumption of fentanyl IVPCA can reflect patient pain response, but this may decrease the analgesic effect of DS. Some objective techniques (e.g., quantitative sensory testing, pain biomarkers) should be evaluated and their potential mentioned in future research. Second, assessments of PONV, dizziness, body temperature and injection site reactions were limited to the hospital stays. Lee et al. [28] reported two patients in the DS Group suffered from injection site swelling that resolved on POD4 and POD8, respectively. Since ultrasound-guided intramuscular DS injection was not mandatory in their study, our use of ultrasound guidance may have reduced such events. However, the lack of follow-up from POD4 to POD7 could have led to an underestimation of the incidence and severity of complications. Third, we also acknowledge the concern regarding whether sesame seed oil is a valid placebo, noting that the DS group received an active analgesic while the Placebo group did not receive an equivalent pain-relief agent. The fourth limitation is the actual amount of Ultracet and acetaminophen consumed. In our study, all patients were prescribed the same postoperative pain medications, but we did not track individual variations in consumption. Such differences in medication adherence may have influenced pain scores. Additionally, after patient discharge from the hospital, we did not differentiate between reported neuropathic and nociceptive pain or both. Improving our understanding of the physiopathology of pain will enhance the efficacy and reliability of treatment during the assessment period [34]. Moreover, our study only

followed patients up to 1 month. Chronic post-surgical pain (CPSP) defined by the International Association for the Study of Pain (IASP) is pain persisting beyond 3 months. Therefore, our findings cannot be extrapolated to CPSP. Lastly, although differences in pain score was statistically significant, NRS values below 3 indicate mild pain, which may not be clinically meaningful. While the DS group had lower pain scores, the clinical impact of this difference requires further investigation.

Conclusions

Our study demonstrated the successful implementation of an alternate MMA strategy that combines peripheral nerve blockade with long-acting DS and NSAIDs to provide effective postoperative analgesia for patients undergoing VATS. This approach effectively reduced the need for opioids and enhances pain control, both during hospitalization and after discharge. Future research should incorporate objective pain assessment methods, extend follow-up durations, and further explore the mechanisms underlying the analgesic effects of DS.

Abbreviations

AM	Ante Meridiem
ASA	American Society of Anesthesiologists Classification
BMI	Body mass index
BIS	Bispectral index
CPSP	Persistent post-surgical pain
DLT	Double-lumen endotracheal tube
DS	Dinalbuphine sebacate
ECG	Electrocardiography
ERAS	Enhanced recovery after surgery
GVL	GlideScope® video laryngoscope
MMA	Multimodal analgesia
NRS	Numerical rating scale
NSAIDs	Nonsteroid anti-inflammatory drugs
PCA	Patient-controlled analgesia
PM	Post Meridiem
POD	Postoperative day
POM	Postoperative month
PONV	Postoperative nausea and vomiting
POW	Postoperative week
RR	Recovery room
VATS	Video-assisted thoracoscopic surgery

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Author contributions

Hung-Te Hsu, Shah-Hwa Chou and Kuang-I Cheng contributed to the study conception and design. Chao-Wei Ma, Po-Chih Chang, Yi-Wei Kuo, Tz-Ping Gau, and Yu-Wei Liu performed material preparation, and data collection. Hung-Te Hsu and Yen-Chin Liup erformed data analysis. Hung-Te Hsu wrote the first draft of the manuscript Hung-Te Hsu, and Tz-Ping Gau prepared Figs. 1, 2 and 3. All authors reviewed and approved the final manuscript.

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Data availability

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

Declarations

Ethics approval and consent to participate

The study protocol was reviewed and approved by the Institutional Review Board of Kaohsiung Medical University Hospital (IRB number KMUHIRB-F(I)-20210087 accepted at 07/05/2021), and was also registered on ClinicalTrials.gov (NCT04962152; Date: 05/07/2021). Written informed consent was obtained from all patients before enrollment in the study. The study was conducted in accordance with the Helsinki Declaration revised in 2013.

Consent for publication

Not applicable.

Prior presentation

Preliminary data from this study were presented in poster form at the Taiwan Pain Society Annual Meeting and Scientific Sessions in Taipei, Taiwan, April 29–30, 2023, and received first place in the clinical poster group.

Competing interests

The authors declare no competing interests.

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