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ORIGINAL RESEARCH

Multimodal Analgesia with Extended-Release Dinalbuphine Sebacate for Perioperative Pain Management in Upper Extremity Trauma Surgery: A Retrospective Comparative Study

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ABSTRACT

Introduction: Patients undergoing upper extremity fracture surgery (UEFS) commonly suffer from unbearable acute pain. Opioids remain the mainstay of moderate to severe pain alleviation, although there is a growing concern regarding the increasing trend in misuse and abuse. This study aimed to observe the safety and efficacy of dinalbuphine sebacate (DS), a novel extended-release analgesic, along with multimodal analgesia (MMA) for post-UEFS pain control.

Methods: We retrospectively reviewed the records of patients undergoing UEFS between August 2020 and January 2021. Eligible patients were included and divided into two groups, depending on the analgesic regimen. In the DS group, 150 mg DS was administered intramuscularly at least 12 h pre-operatively, while in the conventional analgesia (CA) group, 40 mg parecoxib was given within 3 h before surgery. Intraoperative fentanyl administration was guided by the Analgesia Nociception Index System in both groups. For breakthrough pain, fentanyl was used as rescue medicine in the

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postanaesthesia care unit while tramadol and parecoxib were administered in the ward.
Results: Forty-nine patients were allocated to the DS group and 60 patients were allocated to the CA group. In comparison with the CA group, the proportion of patients requiring opioids for breakthrough pain post-operatively was significantly lower in the DS group (fentanyl: 31% vs. 68%, $p < 0.001$; tramadol: 27% vs. 70%, $p < 0.001$). The DS group also consumed lower amounts of post-operative rescue opioids. Furthermore, both mean worst and least pain scores were significantly lower in the DS group from post-operative day (POD) 1 to POD 5. There was no significant difference in intraoperative consumption of fentanyl or incidence of adverse events.
Conclusion: This result suggests that extended-release DS is a suitable analgesic incorporated in MMA and a promising solution to the misuse and abuse of opioids.

Keywords: Dinalbuphine sebacate; Nalbuphine; Opioid analgesics; Post-operative pain; Tramadol; Upper extremity

Key Summary Points

Why carry out this study?

Opioids remain the mainstay of moderate to severe pain alleviation, although there is a growing concern regarding the increasing trend in misuse and abuse.

Dinalbuphine sebacate (DS) is a novel extended-release analgesic, which functions through kappa-opioid receptors and partially antagonises mu-opioid receptors; therefore, it has low addiction potential.

We hypothesised that our multimodal analgesia (MMA) regimen combined with DS will reduce the proportion of patients requiring post-operative opioids and the mean consumption of opioids after upper extremity fracture surgery.

What was learned from the study?

The percentage of patients receiving opioids, mean consumption of opioids and pain intensity were all significantly lower in the DS group.

This result suggests that extended-release DS is a suitable analgesic incorporated in MMA and a promising solution to the misuse and abuse of opioids.

INTRODUCTION

Upper extremity fractures are common and painful injuries, and opioids remain the mainstay after surgery [1]. Opioid misuse and abuse are a global pandemic. In particular, the USA is in the midst of an opioid epidemic [2, 3]; orthopaedic providers are the third highest prescribers by volume of all specialties and have thus played a major role in this public health problem [4]. Given the painful nature of orthopaedic injuries and subsequent repair, patients with orthopaedic trauma in particular are at risk of developing long-term use of opioids [5]. Up to 36% of patients who have experienced musculoskeletal trauma demonstrate the persistent use of opioids 4 months or longer postoperatively compared with a rate of 0.4–3.1% for nontraumatic surgical patients [6]. In 2015, the American Academy of Orthopaedic Surgeons advised the necessity of a comprehensive opioid programme and funding for research into effective alternative pain management and coping strategies to address the opioid epidemic [7].

Dinalbuphine sebacate (DS; NALDEBAIN®, Lumosa Therapeutics, Taipei, Taiwan) is a novel analgesic launched in 2017. It is indicated for moderate to severe post-operative pain relief. With an oil-based formulation and lipophilicity, DS is released slowly and hydrolysed rapidly to nalbuphine by esterase after intramuscular injection [8]. DS is a prodrug of nalbuphine, which functions through kappa-opioid receptors and partially antagonises mu-opioid receptors; therefore, it has low addiction potential

[9, 10]. A previous study reported that through partial mu-opioid receptor antagonism, nalbuphine reduced the common side effects of morphine such as nausea, vomiting and respiratory depression [11]. In addition, a previous phase III study in a population undergoing haemorrhoidectomy demonstrated that the analgesic effect of DS was capable of lasting for about 6 days [12]. The safety and efficacy of DS were also investigated with regard to post-operative pain control of several types of abdominal surgery [13–15].

Currently, multimodal analgesia (MMA), which aims to reduce opioid use, has been shown to provide satisfactory perioperative pain relief with an opioid-sparing effect [16–19]. Epidural analgesia, either continuous or patient controlled; peripheral nerve blocks, either single injection or continuous; acetaminophen; nonsteroidal anti-inflammatory drugs (NSAIDs); gabapentin and ketamine have all been used for this purpose [20]. Many studies have applied MMA in upper extremity trauma surgery and reported good outcomes [21, 22], but few have included DS. To reduce opioid-related adverse effects and the risk of long-term dependence and abuse, DS may be an ideal strategy. We implemented DS in particular in our MMA protocol for perioperative pain management in upper extremity trauma surgery.

In this study, we retrospectively analysed the clinical data from a single centre of patients who underwent operative fixation of upper extremity fractures involving the clavicle through distal radius. We hypothesised that the MMA regimen along with DS will reduce post-operative consumption of opioids and improve pain management.

METHODS

Patients

We retrospectively collected the clinical data of 121 patients between 20 and 80 years of age who underwent operative fixation of upper extremity fractures involving the clavicle through the distal radius in our hospital between 1 August 2020 and 31 January 2021. The study protocol was reviewed and approved by the institutional review board of Tri-Service General Hospital (B202105124) and conducted in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). Written consents were waived. Twelve patients were excluded for the following situations: incomplete post-operative evaluation with a numerical rating scale (NRS), receiving nerve block for pain control, allergy to acetaminophen or non-selective NSAIDs, severe comorbidity (cardiopulmonary disease and cerebrovascular accident) or chronic use of opioids.

Procedure

All patients received general anaesthesia, with American Society of Anesthesiologists physical status classes 1–3. In our clinical practice, intravenously administered dexamethasone (5 mg) was added after tracheal intubation for preventing post-operative nausea and vomiting. To maintain a bispectral index level between 40 and 60 in all patients, sevoflurane in an air–oxygen mixture was administered. Intravenous (IV) administration of intraoperative fentanyl was guided by maintaining the 4-min moving average of the Analgesia Nociception Index (ANI; MetroDoloris Medical Systems, Lille, France) at 50 or greater from intubation to extubation [23]. Boluses of fentanyl 50 μg IV (patients aged less than 50 years) or fentanyl 25 μg IV (patients aged 50 years or older) were administered only if ANI scores decreased to less than 50 and were repeated every 5 min until ANI scores increased to greater than 50.

We categorised the eligible patients in this study into two groups: conventional analgesia (CA) group and dinalbuphine sebatcate (DS) group, depending on the analgesic regimen (Fig. 1). Among both groups, 40 mg parecoxib was intravenously administered within 3 h before surgery in accordance with the internal guidelines of Tri-Service General Hospital. In the DS group, patients were additionally injected with a single dose of 150 mg/2 mL DS into the musculature of the buttock by ultrasound guidance at least 12 h before surgery. For

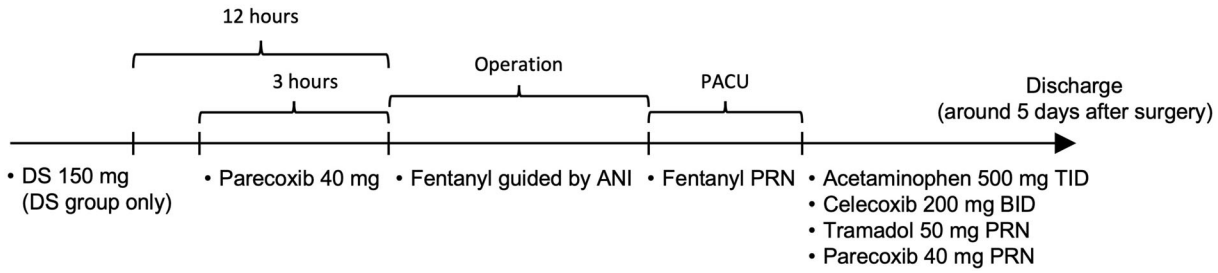

Fig. 1 Multimodal analgesic regimen. *PACU* postanaesthesia care unit

patients with an NRS greater than 3, fentanyl was administered in the postanaesthesia care unit (PACU) at the discretion of the anaesthesiologist. For post-operative pain management, all patients received acetaminophen 500 mg orally three times a day and celecoxib 200 mg twice a day. Either parecoxib or tramadol was prescribed to patients in both groups as rescue analgesics by the surgeons' orders when needed; rescue analgesics (50 mg tramadol or 40 mg parecoxib per time) were recommended for patients with an NRS greater than 3. The quantity and frequency of rescue analgesics were recorded. All patients in the DS group received meclizine hydrochloride 12.5 mg orally every day from day 0 to discharge to prevent DS-induced dizziness.

Data Collection

The primary outcome was quantifying the percentage of patients who required tramadol injection for breakthrough pain within 5 days post-operatively. The secondary outcomes were evaluating the mean analgesic amount administrated in the PACU and wards, post-operative pain intensity during hospital stay, incidence of adverse effects as well as patient satisfaction towards pain management. All the data in this study was retrospectively collected from the medical history of the patients. In accordance with the standard practice in our hospital, pain was assessed in the PACU and at least once daily in the five post-operative days by the 11-point NRS (0 = no pain and 10 = the worst pain imaginable). If patients were discharged early, the assessments were conducted through phone visit. Satisfaction was rated before discharge using a five-point scale (1 = very unsatisfied, 5 = very satisfied). Post-operative complications and analgesic-related side effects were reported either by the patients and/or evaluated by the clinical staff.

Statistics

On the basis of our clinical experience of managing pain with DS, we assumed the difference of the percentage of the population requiring post-operative tramadol between the DS and CA groups to be 35%. With the two-sided significance level at 0.05, power at 95% and allocation ratio at 0.8, the sample size was calculated as 49 in the DS group and 61 in the CA group. Results were presented as mean ± SD. Student *t* test was used for numerical variables, and chi-square test or Fisher exact test was used for categorical variables. One-way analysis of variance was performed to compare the difference in the consumption of analgesics between the DS and CA groups. Statistical significance was defined as $p < 0.05$. The effect sizes towards the pain scores and consumption of opioids were calculated following Cohen's *d* formula: the difference between the means of the DS and CA groups divided by the standard deviation of the CA group. The small, medium and large effect sizes were defined as $d = 0.2$, $d = 0.5$ and $d = 0.8$, respectively. All statistical analyses were performed using the SPSS 21 software package.

RESULTS

Patient Clinical Characteristics

During the study period, a total of 121 patients underwent operative fixation of upper extremity fractures. After exclusion of patients who did not meet the inclusion criteria, 109 patients were included. Forty-nine patients were included in the DS group and 60 patients in the CA group. Table 1 summarises patients' demographics and baseline characteristics. Patient characteristics, including gender, age, weight, body mass index, operation time, postoperative length of hospital stay and surgical characteristics, were similar between the groups. The most common procedures were fixation of the distal radius and proximal humerus fractures.

Table 1 Demographic information and baseline characteristics

	DS (n = 49)	CA (n = 60)	p value
Gender (male/female)	21/28	32/28	0.337
Age	58.5 (13.2)	54.4 (16.5)	0.153
BMI	24.7 (4.4)	24.9 (4.7)	0.798
Height (cm)	163.1 (0.1)	163.5 (0.1)	0.834
Weight (kg)	65.9 (14.5)	66.8 (15.4)	0.760
Operative time (h)	2.8 (0.9)	2.8 (0.7)	0.973
Surgical characteristics			
Clavicle	5 (12%)	7 (10%)	0.984
Proximal humerus	13 (25%)	15 (27%)	
Olecranon	3 (10%)	6 (6%)	
Distal radius	19 (33%)	20 (39%)	
Ulnar	2 (2%)	1 (4%)	
Radius and ulnar	5 (8%)	5 (10%)	
Clavicle and humerus	2 (10%)	6 (4%)	
Length of hospital stay (day)	5.0 (1.6)	5.5 (2.3)	0.226

Data are presented as mean (standard deviation) or number (%). p values < 0.05 were considered statistically significant

BMI body mass index, *CA* conventional analgesia, *DS* dinalbuphine sebacate

Efficacy Outcomes

Figure 2 presents an analysis of perioperative analgesics. In comparison with the CA group, the percentage of patients who postoperatively required tramadol was significantly lower in the DS group (27% vs. 70%, $p < 0.001$; Fig. 2a). The proportion of patients requiring fentanyl in the PACU was also smaller in the DS group (31% vs. 68%, $p < 0.001$; Fig. 2a). Furthermore, the percentage of patients who did not require postoperative analgesics was larger in the DS group than in the CA group (22% vs. 53%, $p = 0.001$; Fig. 2a). The results of opioid consumption were consistent with the pattern of the percentages of patients receiving opioids. The consumption of tramadol in the wards was lower in the DS group (20.4 ± 36.7 mg vs. 58.3 ± 50.6 mg, $p < 0.001$, $d = -0.8$; Fig. 2b). The DS group also consumed a lower amount of fentanyl in the PACU (25.0 ± 49.5 μg vs. 43.0 ± 36.7 μg, $p = 0.037$, $d = -0.5$, Fig. 2b). No significant difference was found in the intraoperative consumption of fentanyl between both groups with ANI-guided administration (170.4 ± 62.6 μg vs. 180.0 ± 66.2 μg, $p = 0.442$, $d = -0.1$; Fig. 2b).

The pain intensity was assessed at least once daily within 5 days after surgery. Significant reductions were observed in the DS group not only for worst pain but also for least pain (Fig. 3). The greatest difference in the worst pain intensity between the DS and CA groups was observed on post-operative day (POD) 1 (3.5 vs. 4.6, $p < 0.001$, $d = -1.2$; Fig. 3a). Within the next 4 days, the mean worst pain intensities of the DS group were still lower than those of the CA group (POD 2: 2.4 ± 1.1 vs. 3.4 ± 0.8, $p < 0.001$, $d = -1.1$; POD 3: 2.1 ± 0.9 vs. 3.1 ± 0.8, $p < 0.001$, $d = -1.1$; POD 4:

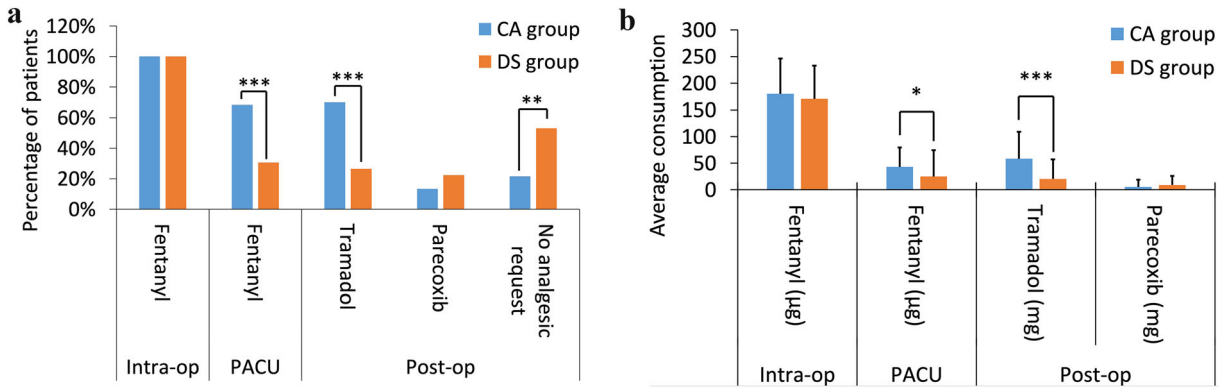

Fig. 2 Summary of analgesic administration. **a** Percentage of patients consuming rescue analgesics. **b** Perioperative consumption of rescue analgesics. Data are presented as percentage or mean with standard deviation. $^{*}p < 0.05$, $^{**}p < 0.01$ and $^{***}p < 0.001$. *Intra-op* intraoperative, *Post-op* post-operative, *PACU* postanaesthesia care unit

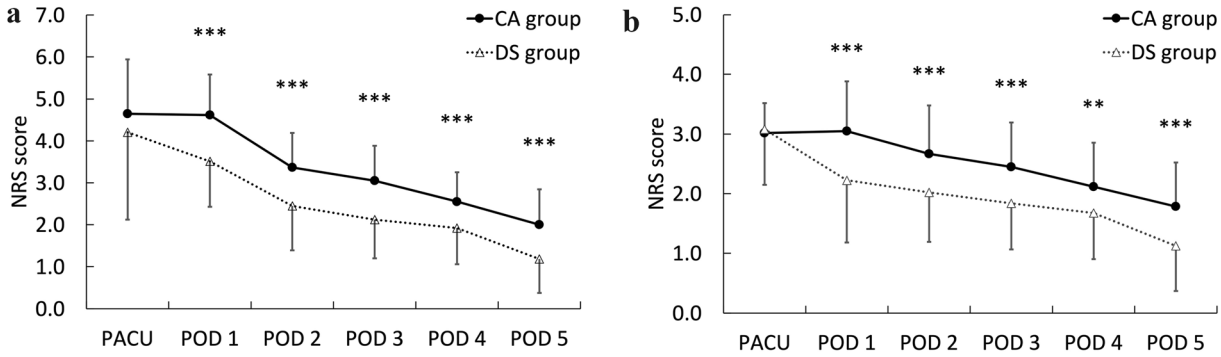

Fig. 3 Post-operative pain intensity. **a** Worst pain assessment. **b** Least pain assessment. Data are presented as mean with standard deviation. $^{**}p < 0.01$ and $^{***}p < 0.001$. *NRS* numerical rating scale, *PACU* postanaesthesia care unit, *POD* post-operative day

1.9 ± 0.9 vs. 2.6 ± 0.7, $d = -0.9$, $p < 0.001$; POD 5: 1.2 ± 0.8 vs. 2.0 ± 0.8, $p < 0.001$, $d = -1.0$; Fig. 3a). A similar pattern was seen in the result of least pain intensity (Fig. 3b). The mean NRS scores of the least pain were lower in the DS group from POD 1 to POD 5 (POD 1: 2.2 ± 1.0 vs. 3.1 ± 0.8, $p < 0.001$, $d = -1.0$; POD 2: 2.0 ± 0.8 vs. 2.7 ± 0.8, $d = -0.8$, $p < 0.001$; POD 3: 1.8 ± 0.8 vs. 2.5 ± 0.7, $d = -0.8$, $p < 0.001$; POD 4: 1.7 ± 0.8 vs. 2.1 ± 0.7, $d = -0.6$, $p < 0.003$ POD 5: 1.1 ± 0.8 vs. 1.8 ± 0.7, $p < 0.001$, $d = -0.9$; Fig. 3b). There was no significant difference in the average pain intensity between both groups during the PACU stay (Fig. 3). Both groups reported great satisfaction with post-operative pain management (4.6 ± 0.5 vs. 4.5 ± 0.5 in DS and CA groups, respectively, $p = 0.413$).

Safety and Adverse Effects

Ten patients reported at least one adverse event in this study, including 6 (12.2%) and 4 (6.6%) patients in the DS and CA groups, respectively. All adverse events were mild to moderate in severity. The most common adverse event was post-operative dizziness, and the incidence was slightly higher in the DS group, without statistical significance (Table 2). One patient in the DS group reported swelling and pain at the injection site that resolved about 1 week after DS injection.

Table 2 Incidence of adverse effects

	DS (n = 49)	CA (n = 60)
Dizziness	5 (10.2%)	3 (5%)
Nausea	1 (2%)	1 (1.6%)
Vomiting	0 (0%)	1 (1.6%)
Injection-site reaction	1 (2%)	0 (0%)

Data are presented as number (%) or mean (standard deviation)
CA conventional analgesia, *DS* dinalbuphine sebacate

DISCUSSION

To the best of our knowledge, this is the first report of the successful implementation of an MMA protocol with long-acting DS for perioperative pain management in upper extremity trauma surgery. The results demonstrated that the pre-emptive intramuscular administration of DS reduced the proportion of patients requiring post-operative tramadol, the mean consumption of opioids and post-operative pain intensity when compared with the CA-administered group. In addition, the percentage of patients without any rescue analgesics was much higher in the DS group.

Orthopaedic operations in upper extremity trauma often result in post-operative pain because of the manipulation of the osseous structures, which makes anaesthesia and post-operative pain management challenging [24]. This issue has been further complicated by the growing opioid epidemic in the USA and the increasing insights into its detrimental effects on society [5]. The use of MMA for acute pain management is becoming a focus in upper extremity trauma surgery, as the reduction in opioid prescription and consumption continues to be a focus in the perioperative setting [21]. Simple interventions such as patient education handouts with regard to the safe and effective use of opioids after a hand surgical procedure have shown promise in reducing opioid consumption [22]. Recent guidelines published by a joint committee of multiple anaesthesia specialty societies endorsed the use of acetaminophen, NSAIDs and gabapentinoids in multimodal regimens [25]. However, their recommendations pertaining to orthopaedic practice were limited to total hip arthroplasty, total knee arthroplasty and spinal fusions, for which the most level I evidence exists. In a prospective study of 150 patients who underwent shoulder arthroplasty, McLaughlin et al. reported decreased pain, overall opioid consumption and shorter hospital stays for those administered a regimen of scheduled pre- and post-operative acetaminophen, celecoxib and gabapentin [26]. Among 59 patients who received volar plating of the distal radius, Nelson and La tested a pain control strategy consisting of pre- and post-operative acetaminophen and celecoxib, patient counselling, peripheral nerve blocks, intraoperative local anaesthetic infiltration, as-needed hydrocodone–acetaminophen and a post-operative phone call [27]. Although this study did not include a control group, the findings were notable for an average opioid consumption of only 0.68 pills and no refill requests. Remarkably, 72% of the patients used no narcotics [27]. Studies of upper extremity regimens, although less robust, appear to reflect similar medication preferences.

In collaboration with orthopaedic surgeons, our institution has established an MMA protocol for patients undergoing upper extremity trauma surgery. As in our conventional MMA protocol, a combination of intravenously administered parecoxib before surgery and oral analgesics, including acetaminophen and celecoxib, were used during the entire perioperative period for preventive pain management. Long-acting DS administered intramuscularly was recently introduced in Taiwan as a slow release nalbuphine prodrug with a long duration of action; it delivers and maintains an effective blood level for approximately 6 days [28]. This regimen provides pre-emptive and preventive analgesia. It not only covers the post-operative but also the whole perioperative pain control for at least 5 days after surgery, in combination with oral analgesics, like acetaminophen and NSAIDs or COX-2 inhibitors, which cover the operative pain after patient discharge with no opioid prescription. Further, the long-acting opioid nalbuphine, DS, is less dependent and

has less addiction potential than other μ-opioid drugs in the clinic. Therefore, it shows potential as an ideal analgesic as part of the MMA protocol. In this study, we demonstrated that patients undergoing upper extremity fracture surgery (UEFS) with this multimodal analgesic regimen emphasising intramuscular DS experienced a significant improvement in post-operative analgesia, including lower NRS pain scores and lower opioid requirements with an opioid-sparing effect. Furthermore, the analgesics (acetaminophen, celecoxib and parecoxib) used in our MMA protocol not only provided an analgesic effect by themselves but also enhanced the analgesia of long-acting DS. Further studies should be designed to investigate the interactions between long-acting DS and other analgesics.

The use of single-dose extended release of DS resulted in a relatively low maximum plasma concentration of nalbuphine [29], and the routine administration of antiemetics (dexamethasone and meclizine hydrochloride) led to a lower trend in dizziness, nausea and vomiting observed in our study. In a previous report of intramuscular DS, injection-site reactions such pain, erythema and swelling were commonly reported adverse effects (10–27.5%) [12, 14, 15]. In our DS group, only one patient (2%) experienced swelling with pain at the injection site. We believe that this difference resulted from the use of ultrasound-guided DS injection correctly into gluteal muscle.

Because of concerns regarding the fact that DS is a kappa-opioid receptor agonist and mu-opioid receptor antagonist, we used the ANI to guide the administration of intraoperative fentanyl. Because ANI scores reflect changes in the nociceptive level with more sensitivity than traditional parameters such as heart rate and blood pressure, we used the ANI to determine the potential impact of DS on perioperative anaesthesia usage [30, 31]. Even though DS was administered before surgery, we found no difference in fentanyl usage during surgery between the two groups, which is consistent with previous reports [13–15].

Perioperative regional analgesia with ultrasound-guided peripheral nerve blocks has been reported to improve patients' satisfaction with post-operative pain management and facilitate early rehabilitation [32, 33]. Therefore, perineural analgesia is currently favoured for UEFS and post-operative pain management as part of the MMA regimen [18, 20, 21]. Multiple randomised controlled trials have consistently demonstrated that peripheral nerve block provides superior analgesia compared with general anaesthesia in the setting of upper extremity surgery [34]. However, in a 2015 systematic review and meta-analysis of interscalene block for shoulder surgery, Abdallah and colleagues did not find the opioid-sparing benefits to persist beyond the first 24 h, while introducing the potential for rebound pain when the nerve block wore off [35]. Furthermore, the success of nerve block relies on great skills and extensive experience [36]. DS, by contrast, is easier to use. In the present study, it was suggested that patients receiving a single intramuscular injection of DS required less opioids postoperatively. Further study should be conducted to evaluate the potential of integrating DS in regional analgesia combined with conventional analgesic procedures or, especially, the nerve block. With the extended release of DS, the rebound pain caused by nerve block may be resolved.

The retrospective study design might have led to bias in terms of standardisation and comparability of the study groups. For the purpose of this study, a retrospective analysis of data offered a major advantage, namely, that anaesthetic management was performed by the attending anaesthesiologist according to clinical demands and the patients themselves self-rated their pain score with analgesic requirements. This study, conducted under real clinical conditions, reflects more precisely the clinically relevant benefit that may be expected with the use of new drugs or devices.

CONCLUSIONS

We demonstrated this successful MMA protocol with DS in upper extremity trauma surgery. This protocol included ultrasound-guided intramuscular DS and other analgesics (acetaminophen, celecoxib and parecoxib) to achieve good post-operative analgesia with an opioid-sparing

effect. The results of our study show that the slow release of nalbuphine, DS, may play an important role in perioperative MMA. A large-scale clinical trial is required to show its role in the MMA regimen.

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Author Contributions. Conceptualisation: Chueng-He Lu; Methodology: Chueng-He Lu and Zhi-Hong Zheng; Formal analysis and investigation: Zhi-Hong Zheng, Tsu-Te Yeh, Chun-Chang Yeh, Po-An Lin and Po-Yu Lee; Writing—original draft preparation: Chueng-He Lu and Zhi-Hong Zheng; Writing—review and editing: Zhi-Hong Zheng, Tsu-Te Yeh, Chun-Chang Yeh, Po-An Lin, Chih-Shung Wong, Po-Yu Lee and Chueng-He Lu; Supervision: Chueng-He Lu and Chih-Shung Wong.

Disclosures. Zhi-Hong Zheng, Tsu-Te Yeh, Chun-Chang Yeh, Po-An Lin, Chih-Shung Wong, Po-Yu Lee and Chueng-He Lu declare that they have no conflict of interest.

Compliance with Ethics Guidelines. The study protocol was reviewed and approved by the institutional review board of Tri-Service General Hospital (B202105124), which waived the informed consent due to the retrospective nature of study. The study was conducted in accordance with the Helsinki Declaration revised in 2013.

Data Availability. The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

REFERENCES

1. Cunningham DJ, LaRose MA, Klifto CS, Gage MJ. Mental health and substance use affect perioperative opioid demand in upper extremity trauma surgery. J Shoulder Elbow Surg. 2021;30:e114–20. https://doi.org/10.1016/j.jse.2020.06.024.

2. Dart RC, Surratt HL, Cicero TJ, et al. Trends in opioid analgesic abuse and mortality in the United States. N Engl J Med. 2015;372:241–8. https://doi.org/10.1056/NEJMsa1406143.

3. Morris BJ, Mir HR. The opioid epidemic: impact on orthopaedic surgery. J Am Acad Orthop Surg. 2015;23:267–71. https://doi.org/10.5435/JAAOS-D-14-00163.

4. Volkow ND, McLellan TA, Cotto JH, Karithanom M, Weiss SR. Characteristics of opioid prescriptions in 2009. JAMA. 2011;305:1299–301. https://doi.org/10.1001/jama.2011.401.

5. Gerbershagen HJ, Aduckathil S, van Wijck AJ, Peelen LM, Kalkman CJ, Meissner W. Pain intensity on the first day after surgery: a prospective cohort study comparing 179 surgical procedures. Anesthesiology. 2013;118:934–44. https://doi.org/10.1097/ALN.0b013e31828866b3.

6. Rosenbloom BN, McCartney CJL, Canzian S, Kreder HJ, Katz J. Predictors of prescription opioid use 4 months after traumatic musculoskeletal injury and corrective surgery: a prospective study. J Pain. 2017;18:956–63. https://doi.org/10.1016/j.jpain.2017.03.006.

7. American Academy of Orthopaedic Surgeons. Information statement: opioid use, misuse, and abuse in orthopaedic practice. Illinois, United States: American Academy of Orthopaedic Surgeons; 2015. https://aaos.org/globalassets/about/bylaws-library/information-statements/1045-opioid-use-misuse-and-abuse-in-practice.pdf. Accessed 3 Oct 2021.

8. Pao LH, Hsiong CH, Hu OY, Wang JJ, Ho ST. In vitro and in vivo evaluation of the metabolism and pharmacokinetics of sebacoyl dinalbuphine. Drug Metab Dispos. 2005;33:395–402. https://doi.org/10.1124/dmd.104.002451.

9. Houlihan KP, Mitchell RG, Flapan AD, Steedman DJ. Excessive morphine requirements after prehospital nalbuphine analgesia. J Accid Emerg Med. 1999;16:29–31. https://doi.org/10.1136/emj.16.1.29.

10. Peachey JE. Clinical observations of agonist-antagonist analgesic dependence. Drug Alcohol Depend. 1987;20:347–65. https://doi.org/10.1016/0376-8716(87)90008-1.

11. Yeh YC, Lin TF, Lin FS, Wang YP, Lin CJ, Sun WZ. Combination of opioid agonist and agonist-antagonist: patient-controlled analgesia requirement and adverse events among different-ratio morphine and nalbuphine admixtures for postoperative pain. Br J Anaesth. 2008;101:542–8. https://doi.org/10.1093/bja/aen213.

12. Yeh CY, Jao SW, Chen JS, et al. Sebacoyl dinalbuphine ester extended-release injection for long-acting analgesia: a multicenter, randomized, double-blind, and placebo-controlled study in hemorrhoidectomy patients. Clin J Pain. 2017;33:429–34. https://doi.org/10.1097/AJP.0000000000000417.

13. Chang TK, Huang CW, Su WC, et al. Extended-release dinalbuphine sebacate versus intravenous patient-controlled analgesia with fentanyl for postoperative moderate-to-severe pain: a randomized controlled trial. Pain Ther. 2020;9:671–81. https://doi.org/10.1007/s40122-020-00197-x.

14. Lee SO, Huang LP, Wong CS. Preoperative administration of extended-release dinalbuphine sebacate compares with morphine for post-laparoscopic cholecystectomy pain management: a randomized study. J Pain Res. 2020;13:2247–53. https://doi.org/10.2147/JPR.S263315.

15. Chang TC, Chen MY, Chen WC, Chou HH. Comparison of the efficacy and safety of dinalbuphine sebacate, patient-controlled analgesia, and conventional analgesia after laparotomy for gynecologic cancers: a retrospective study. J Pain Res. 2021;14:1763–71. https://doi.org/10.2147/JPR.S314304.

16. Hollmann MW, Rathmell JP, Lirk P. Optimal postoperative pain management: redefining the role for opioids. Lancet. 2019;393:1483–5. https://doi.org/10.1016/S0140-6736(19)30854-2.

17. Beverly A, Kaye AD, Ljungqvist O, Urman RD. Essential elements of multimodal analgesia in enhanced recovery after surgery (ERAS) guidelines. Anesthesiol Clin. 2017;35:e115–43. https://doi.org/10.1016/j.anclin.2017.01.018.

18. Pulos BP, Bowers MR, Shin AY, Pulos N. Opioid-sparing pain management in upper extremity surgery: part 1: role of the surgeon and anesthesiologist. J Hand Surg Am. 2019;44:787–91. https://doi.org/10.1016/j.jhsa.2019.01.020.

19. Echeverria-Villalobos M, Stoicea N, Todeschini AB, et al. Enhanced recovery after surgery (ERAS): a perspective review of postoperative pain management under ERAS pathways and its role on opioid crisis in the United States. Clin J Pain. 2020;36:219–26. https://doi.org/10.1097/AJP.0000000000000792.

20. Kaye AD, Urman RD, Cornett EM, et al. Enhanced recovery pathways in orthopedic surgery. J Anaesthesiol Clin Pharmacol. 2019;35:S35–9. https://doi.org/10.4103/joacp.JOACP_35_18.

21. Stewart TM, Pulos N, Curry TB, Gazelka HM, Brown MJ, Shin AY. Team approach: multimodal perioperative pain management in upper-extremity surgery: combating the opioid epidemic. JBJS Rev. 2018;6: e5. https://doi.org/10.2106/JBJS.RVW.17.00190.

22. Dwyer CL, Soong M, Hunter A, Dashe J, Tolo E, Kasparyan NG. Prospective evaluation of an opioid reduction protocol in hand surgery. J Hand Surg Am. 2018;43:516–22. https://doi.org/10.1016/j.jhsa.2018.01.021.

23. Anderson TA, Segaran JR, Toda C, Sabouri AS, De Jonckheere J. High-frequency heart rate variability index: a prospective, observational trial assessing utility as a marker for the balance between analgesia and nociception under general anesthesia. Anesth Analg. 2020;130:1045–53. https://doi.org/10.1213/ANE.0000000000004180.

24. Labrum JT 4th, Ilyas AM. Perioperative pain control in upper extremity surgery: prescribing patterns, recent developments, and opioid-sparing treatment

strategies. Hand (N Y). 2019;14:439–44. https://doi.org/10.1177/1558944718787262.

25. Chou R, Gordon DB, de Leon-Casasola OA, et al. Management of postoperative pain: a clinical practice guideline from the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council. J Pain. 2016;17:131–57. https://doi.org/10.1016/j.jpain.2015.12.008.

26. McLaughlin DC, Cheah JW, Aleshi P, Zhang AL, Ma CB, Feeley BT. Multimodal analgesia decreases opioid consumption after shoulder arthroplasty: a prospective cohort study. J Shoulder Elbow Surg. 2018;27:686–91. https://doi.org/10.1016/j.jse.2017.11.015.

27. Nelson DL, La B. Demonstration of an effective postoperative pain management protocol in distal radius fractures: level 4 evidence. J Hand Surg Am. 2013;38:e6-7. https://doi.org/10.1016/j.jhsa.2013.08.012.

28. Tien YE, Huang WC, Kuo HY, et al. Pharmacokinetics of dinalbuphine sebacate and nalbuphine in human after intramuscular injection of dinalbuphine sebacate in an extended-release formulation. Biopharm Drug Dispos. 2017;38:494–7. https://doi.org/10.1002/bdd.2088.

29. Huang PW, Liu HT, Hsiong CH, et al. Simultaneous determination of nalbuphine and its prodrug sebacoly dinalbuphine ester in human plasma by ultra-performance liquid chromatography-tandem mass spectrometry and its application to pharmacokinetic study in humans. Biomed Chromatogr. 2013;27:831–7. https://doi.org/10.1002/bmc.2867.

30. Jeanne M, Clément C, De Jonckheere J, Logier R, Tavernier B. Variations of the analgesia nociception index during general anaesthesia for laparoscopic abdominal surgery. J Clin Monit Comput. 2012;26:289–94. https://doi.org/10.1007/s10877-012-9354-0.

31. Gruenewald M, Ilies C, Herz J, et al. Influence of nociceptive stimulation on analgesia nociception index (ANI) during propofol-remifentanil anaesthesia. Br J Anaesth. 2013;110:1024–30. https://doi.org/10.1093/bja/aet019.

32. Heesen M, Klimek M, Imberger G, Hoeks SE, Rossaint R, Straube S. Co-administration of dexamethasone with peripheral nerve block: intravenous vs perineural application: systematic review, meta-analysis, meta-regression and trial-sequential analysis. Br J Anaesth. 2018;120:212–27. https://doi.org/10.1016/j.bja.2017.11.062.

33. Smith LM, Cozowicz C, Uda Y, Memtsoudis SG, Barrington MJ. Neuraxial and combined neuraxial/general anesthesia compared to general anesthesia for major truncal and lower limb surgery: a systematic review and meta-analysis. Anesth Analg. 2017;125:1931–45. https://doi.org/10.1213/ANE.0000000000002069.

34. Liu SS, Strodtbeck WM, Richman JM, Wu CL. A comparison of regional versus general anesthesia for ambulatory anesthesia: a meta-analysis of randomized controlled trials. Anesth Analg. 2005;101:1634–42. https://doi.org/10.1213/01.ANE.0000180829.70036.4F.

35. Abdallah FW, Halpern SH, Aoyama K, Brull R. Will the real benefits of single-shot interscalene block please stand up? a systematic review and meta-analysis. Anesth Analg. 2015;120:1114–29. https://doi.org/10.1213/ANE.0000000000000688.

36. Yeniocak T, Canbolat N. Retrospective analysis of ultrasound-guided infraclavicular block: effect of experience of anesthesiologists on volume of local anesthetic administered. Pain Res Manag. 2019;2019:4846956. https://doi.org/10.1155/2019/4846956.