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# Multimodal analgesia as part of enhanced recovery after surgery in colorectal surgery

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## Abstract

*Introduction:* Multimodal analgesia regime in enhanced recovery after surgery (ERAS) protocol is associated with fewer perioperative complications, shorter hospital stays, and reduced opioid dependence. Although ERAS strategies have been widely accepted and implemented in current practice, there is limited data regarding its application and outcomes in the Malaysian population, particularly in colorectal surgeries. Hence, this study was conducted to examine postoperative pain scores after implementing a multimodal analgesia regime as per ERAS anaesthesia protocol.

*Methods:* This is a retrospective study using data collection forms. Data were collected from the case notes of patients who underwent colorectal surgery complying with the ERAS anaesthesia protocol from January 2022 to December 2023. Pain score was assessed when the patient arrived at recovery bay, subsequently reassessed at 2 hours postoperative, 6 hours postoperative, 12 hours postoperative, 1 day postoperative and finally on postoperative day 2.

*Results:* A total of 139 samples were recruited in this retrospective study. The median postoperative pain scores at rest were consistently 0 from arrival at recovery bay to postoperative day 2. On the other hand, the median pain score upon movement

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was 1 (range 0–3) when patients reached the recovery bay, and persistently 3 during postoperative 2 hours, 6 hours, and 12 hours, after which the median pain score upon movement became 2 on postoperative day 1 and day 2.

*Conclusions*: Multimodal analgesia in line with the ERAS protocol in colorectal surgeries is feasible, safe and efficient.

*Keywords:* colorectal surgery, enhanced recovery after surgery, multimodal analgesia

## Introduction

The enhanced recovery after surgery (ERAS) protocol is a protocol consisting of evidence-based items designed to reduce perioperative stress, maintain postoperative physiological function, and accelerate recovery after surgery. The multimodal approach has been shown to improve recovery, reduce morbidity, and shorten length of stay after colorectal surgery.[1]

One of the most important components of ERAS is multimodal analgesia. In a national survey, 80% of patients undergoing surgery report pain that is of moderate, severe, or extreme intensity in the first 2 weeks following surgery. Thus, postoperative pain management is a major concern for patients undergoing surgery.[2]

The opioid-based analgesia regime is the primary analgesia modality for many anaesthesiologists regardless of the type of surgical procedure. However, opioid-related adverse events are common, namely, respiratory depression, drowsiness, sedation, postoperative nausea and vomiting, pruritus, urinary retention, and ileus. All of these may lead to morbidity, mortality, prolonged length of stay, increased healthcare costs, and development of chronic pain.[1] Apart from perioperative complications, opioid-based analgesia is also recognized as one of the potential causes of the opioid crisis in America, which involves 2 million individuals with opioid-use disorder and a substantial economic cost estimated at nearly US$80 billion annually.[3]

The ERAS Society strongly recommends a multimodal analgesia regime in their guidelines. The principle of multimodal analgesia is to use different classes of medications to act on multiple pain receptors, aiming to achieve optimum pain control while minimising the side effects of each drug. Multiple studies have yielded

promising results where a multimodal analgesia regime is associated with early mobilisation, fast return of bowel function, fewer perioperative complications, and reduction in length of stay.[1]

The ERAS service was started in Hospital Sultanah Aminah in 2018 with the collaboration between the Department of Anaesthesia and the Department of General Surgery. A well-written ERAS protocol has been implemented and adapted to local practices since then. A local study showed that the length of hospital stay decreased from 6 days to 5 days after the implementation of the ERAS protocol. Besides that, the readmission rate decreased significantly from 17.4% to 8.6% and zero mortality was recorded throughout the study period.[4]

While most studies have concluded that multimodal analgesia is beneficial, it has significant limitations, particularly in elderly patients due to the potential risks of polypharmacy. Elderly patients often have suboptimal liver and kidney function, leading to altered drug metabolism and exacerbation of the drugs' adverse effects. Administration of multiple drugs also increases the risk of drug-drug interactions. Some novel drug delivery systems, such as controlled-release hydrogels and nanoparticles, have been suggested to allow more targeted and sustained release of medication, thus minimising the associated side effects while optimising pain control.[5]

Although ERAS strategies have been widely accepted and implemented in current practice, there is limited data regarding their application and outcomes in the Malaysian population, particularly in colorectal surgeries. Hence, this study was conducted to examine postoperative pain scores after implementing multimodal analgesia regime as per the ERAS anaesthesia protocol.

## Methods

This is a retrospective study conducted in Hospital Sultanah Aminah Johor Bahru between January 2022 and December 2023. Ethical approval was obtained from the Medical Research Ethics Committee, Ministry of Health Malaysia (Ethics approval number: 24-00484-KIQ).

A list of patients who underwent colorectal surgery complying with the ERAS anaesthesia protocol from January 2022 to December 2023 was obtained from the operation theatre office. Patients 18 years of age and above were included in the study. Exclusion criteria were patients who were given long-acting opioids during the intraoperative or postoperative period, inadequate or missing patient from the case notes, and patients who were admitted to the Post-Anaesthesia Care Unit (PACU) or Intensive Care Unit (ICU) postoperatively.

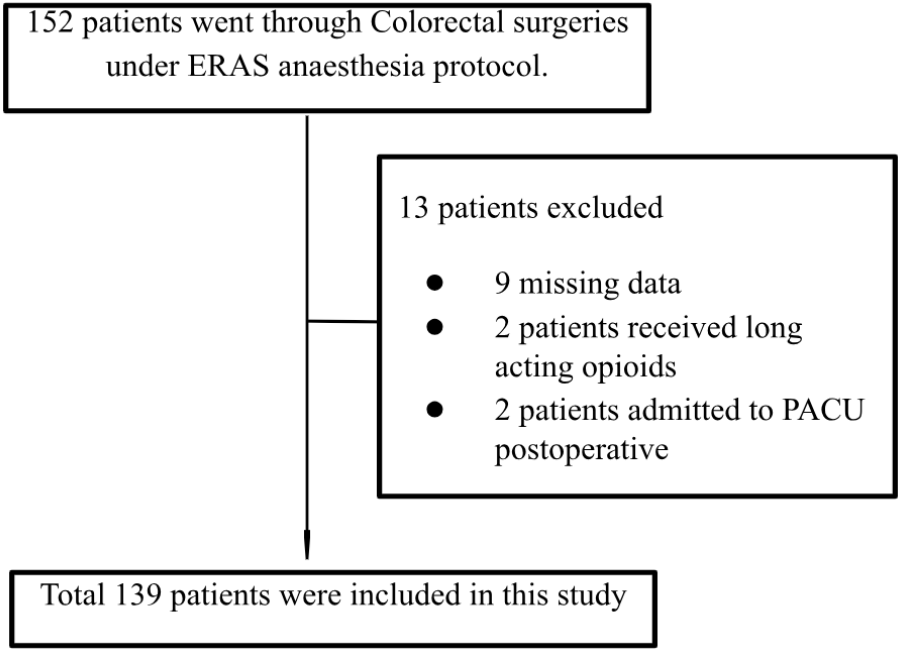


*Fig. 1.* Patient recruitment process.

A total of 152 patients were identified. However, 9 of them were excluded due to missing data. Compliance for documenting postoperative pain score was 94%. Two patients were excluded because they received long-acting opioids, and another 2 patients were excluded as they were admitted to PACU postoperatively. Therefore, a total of 139 cases were recruited in this retrospective study (Fig. 1).

Patient data were collected from their case notes and recorded in the data collection form (Appendix). An anonymous study identification was assigned to each patient. Personal information such as name, hospital registration number, and identity number were not recorded. Age, medical illness, American Society of Anesthesiologists (ASA) status, type of surgical procedure, and pain score on arrival at recovery bay, 6 hours postoperative, 12 hours postoperative, postoperative day 1, and postoperative day 2 were among the data collected.

All patients recruited under the ERAS program underwent induction and maintenance of anaesthesia as per protocol. Mandatory analgesics such as intravenous (IV) paracetamol, IV magnesium sulphate, IV dexamethasone, and IV parecoxib were given to all patients unless contraindicated. Analgesia infusion choice such as thoracic epidural analgesia, IV lignocaine infusion, IV ketamine infusion, and targeted controlled infusion (TCI) remifentanil would be decided by the anaesthetist of the case. Multilayer local anaesthesia infiltration upon closing of the abdomen and a continuous wound infiltration (CWI) catheter would be administered by the surgeon upon closing of the abdomen.

Postoperatively, patients were monitored in the recovery area of operation theatre for 30 minutes. Oral analgesics such as tablet paracetamol and tablet etoricoxib were prescribed before discharging patients back to the ward.

A visual analog scale was used to evaluate the patient's pain. The pain score was assessed and documented when the patient arrived at the recovery bay, postoperative 2 hours, postoperative 6 hours, postoperative 12 hours, postoperative day 1, and postoperative day 2.

IV fentanyl 50 microgram was the choice of rescue analgesia for breakthrough pain until the patient's pain score reduced to less than four. If pain control was still inadequate, patient-controlled analgesia (PCA) fentanyl would be offered to the patient.

### Statistical analysis

The data were analysed using SPSS 26 (SPSS Inc., Chicago, IL, USA). We performed descriptive statistics (mean and standard deviation (SD)) on patients' demographic variables. Parametric data are presented as mean ± SD, whereas skewed data sets are shown in the median (interquartile range).

## Results

A total of 139 cases were recruited in this retrospective study. Table 1 summarises the demographic data, type and duration of surgery, and ASA category of the patients. Table 2 presents the types of perioperative analgesia for all patients included in the study. Interestingly, 20 patients did not receive any analgesia infusion. However, almost half of these patients required rescue analgesia at recovery bay and 2 of them were on PCA fentanyl in the ward.

*Table 1.* Demographic data of patients

| Demographic data | Number of patients, *n* = 139 |
|---|---|
| Age | 63 (55–71) |
| Gender | |
| Male | 92 (66.2%) |
| Female | 47 (33.8%) |
| Type of surgery | |
| Open surgery | 115 (80.42%) |
| Laparoscopic surgery | 24 (17.3%) |
| Duration of surgery | 150 minutes (127–186) |
| American Society of Anaesthesiologists category | |
| I | 17 (12.2%) |
| II | 113 (79.9%) |
| III | 11 (6.5%) |
| IV | 2 (1.40%) |

*Table 2.* Perioperative analgesia

| Choice of adjunct analgesia | Number of patients, *n* = 139 (%) | Number of patients requiring rescue analgesia* in recovery | Number of patients requiring PCA fentanyl |
|---|---|---|---|
| Lignocaine infusion | 82 (59.0) | 19 | 3 |
| Lignocaine + ketamine infusion | 17 (12.2) | 2 | 1 |
| Lignocaine + remifentanil infusion | 5 (3.6) | 1 | 1 |
| Lignocaine + ketamine + remifentanil infusion | 3 (2.2) | 2 | 0 |
| Ketamine infusion | 1 (0.7) | 0 | 0 |
| Remifentanil infusion | 8 (5.8) | 4 | 3 |
| Not on analgesia infusion | 20 (14.4) | 8 | 2 |
| Epidural | 1 (0.7) | 0 | 0 |

*IV fentanyl 25–100 µg

*Table 3.* Summary of postoperative pain score

| Postoperative duration | Median pain score (interquartile range) | |
|---|---|---|
| | At rest | Upon movement |
| Upon arrival to recovery bay | 0 (0–2) | 1 (0–4) |
| 2 hours | 0 (0–3) | 3 (0–4) |
| 6 hours | 0 (0–2) | 3 (2–4) |
| 12 hours | 0 (0–1) | 3 (2–3) |
| 1 day | 0 (0–2) | 2 (1–4) |
| 2 days | 0 (0–1) | 2 (0–3) |

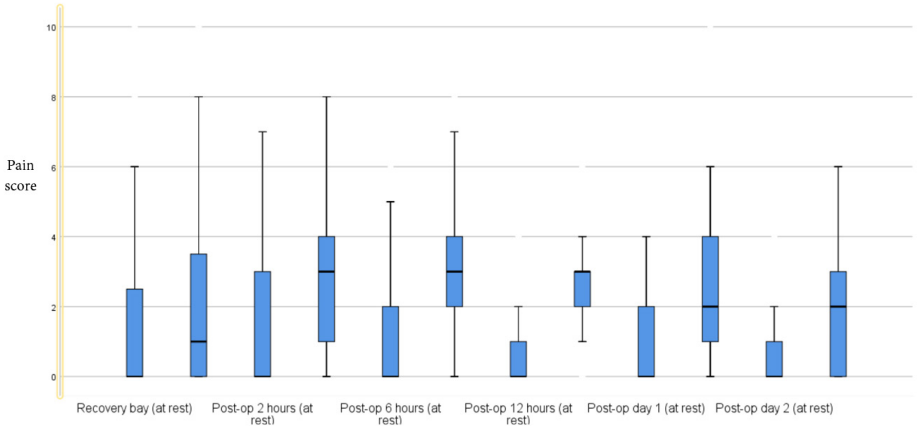


*Fig. 2.* Summary of postoperative pain score

Table 3 and Figure 2 show the summary of postoperative pain score from the patients' arrival at the recovery bay post operation up to postoperative day 2. The Kolmogorov-Smirnov test was performed to test on normality of the data, which reflected that all the postoperative pain score data were non-parametric data with $p < 0.05$. The median postoperative pain scores at rest were consistently 0 from arrival at recovery bay to postoperative day 2. On the other hand, the median pain score upon movement was 1 (range 0–3) when the patients reached the recovery bay, persistently 3 at postoperative 2 hours, 6 hours, and 12 hours, after which the median pain score upon movement became 2 on postoperative days 1 and 2. Throughout the postoperative period, the median pain scores at rest and upon movement were less than 4, which did not require any further pain intervention.

## Discussion

The opioid crisis has significantly impacted the healthcare system in the United States leading to increased addiction rate, overdoses, and deaths.[3] Fortunately, the opioid crisis is not happening in Malaysia yet, but it is a growing concern over widespread use of opioids perioperatively. The postoperative period is a particularly vulnerable time as opioids have traditionally been used for pain management. Thus, multimodal analgesia is emerging as an alternative for managing postoperative pain effectively without relying heavily on opioids.

The ERAS Protocol consists of 20 components that involve multiple teams including surgeons, anaesthesiologists, nurses, dieticians, physiotherapists and others. However, the involvement of a multidisciplinary team requires a higher level

of communication to ensure good collaboration between different teams in terms of preoperative nutrition optimisation, intraoperative fluid management, perioperative pain management, and postoperative rehabilitation. This has not only increased the difficulty to ensure compliance in every step but also created more challenges to conduct a study or audit for systematic performance assessment. The primary outcome in studies related to ERAS has been the length of hospital stay.[4,5] To date, almost none of the studies conducted in Malaysia examine the pain score after implementing a multimodal analgesia regime as per ERAS protocol for colorectal surgeries.

The involvement of multiple teams in ERAS and low compliance with the protocol are the main reasons for the lack of data, especially in Malaysia, despite the ERAS protocol being widely accepted and practised locally. Despite the difficulties, the importance of complying with the protocol needs to be highlighted and re-emphasised as it significantly improves patients' clinical outcomes.[5]

The latest ERAS guidelines in colorectal surgeries recommend multimodal opioid-sparing analgesia to avoid the untoward effects of opioids. In our centre, IV lidocaine infusion is one of the non-opioid analgesics frequently used in surgeries compliant with the ERAS protocol. In addition to its well-known direct local anaesthetic effect, it also has antinociceptive, antihyperalgesic, and anti-inflammatory properties. Lidocaine infusion has been proven to reduce postoperative pain, particularly in the early postoperative period after laparoscopic and open abdominal surgery.[6] The recommended loading dose for IV lidocaine is 1.5 mg/kg administered over 10 minutes, then starting the infusion at 1.5 mg/kg/hour. These doses are generally safe after considering factors affecting lidocaine metabolism and clearance, such as heart failure, hepatic and renal impairment, volume of distribution, protein binding, and drug-drug interaction. Despite widespread use of IV lidocaine infusion in our centre, there has been no occurrence of local anaesthetic systemic toxicity.[7]

Ketamine is one of the options in the multimodal analgesia regime. It has a strong analgesic effect but only affects minimally on respiratory depression. Ketamine infusion has been proven to decrease postoperative opioid requirements, reduce postoperative pain scores, and increase time to first rescue analgesia. Ketamine is associated with the neuropsychiatric manifestation postoperatively, but the incidence of this side effects varies with the total dose of ketamine and the timing of ketamine administration.[8] We have frequently added a ketamine infusion if there was unsatisfactory pain control from lidocaine infusion alone and so far there have been no significant adverse events, such as delirium, that required intervention at our centre.

Remifentanil has unique pharmacokinetic profiles where it has a very short context sensitive half-time despite being given as a prolonged infusion. Thus, it is one of the preferred medications to use during induction of anaesthesia as an adjunct for monitored sedation as well as for postoperative pain management. However, remifentanil infusion is associated with opioid-induced hyperalgesia (OIH) in a dose-dependent fashion. One systematic review has reported OIH even at doses as low as 0.1 μg/kg/min.[9] Hence, remifentanil infusion is less favoured in our centre.

Thoracic epidural analgesia is recognized as the gold standard for patients undergoing open colorectal surgery as it not only offers excellent pain control but also reduces the neuroendocrine and metabolic responses to surgery.[1] Although many advantages can be observed from thoracic epidural analgesia, it is not without complications. Examples of complications that have been reported include hypotension, urinary retention, partial or patchy block and, in rare cases, devastating neurological injuries such as epidural hematoma.[10] A case of epidural abscess that led to permanent sequelae was observed with an occurrence of 1 in 3126 in a single-centre study in Italy.[11] Besides that, thoracic epidural analgesia is unable to block sacral nerves adequately; thus, it may not be suitable for all colorectal surgeries, such as abdominal-perineal surgery.

All our patients in the ERAS program were offered CWI. Multiple studies have shown that CWI is able to provide adequate pain relief, reduce opioid consumption, reduce opioid-related complications, and at the same time accelerate postoperative recovery.[12] A systematic review performed in 2013 showed that there were no significant differences in postoperative pain scores comparing epidural analgesia and CWI following abdominal surgeries.[13] Thus, the CWI technique is preferred in our centre, as it has multiple benefits that are comparable to epidural analgesia but avoids hazardous complications associated with thoracic epidural analgesia.

This study has several limitations. Firstly, the analgesia infusions were not standardised in all patients. The choice of analgesia infusion depended on the anaesthesiologist in charge of the case and patients received different types of analgesia regimes intraoperatively, which has limited the generalisability of our findings. Secondly, the types of surgery were not equally distributed in our study, in which 82.7% of patients underwent laparotomy while the rest underwent laparoscopic surgery. Pain intensity in laparotomy surgery is more severe than in laparoscopic surgery. Nevertheless, our study shows a promising result in postoperative pain score with the multimodal analgesia regime.

The ERAS protocol has not only demonstrated good clinical outcomes but also reduced the average length of hospital stay, promoted hospital bed turnover rate, and reduced the healthcare cost.[14] Multimodal analgesia certainly is one of the core components that makes ERAS a successful program. This study shows a good outcome following a multimodal analgesia regime in colorectal surgery. However, the level of evidence is limited by its retrospective design. More prospective studies with standardised interventions and control groups shall be done in future to examine the outcome of multimodal analgesia protocols and provide stronger evidence of efficacy.

## Conclusion

Based on the findings of this retrospective study, we conclude that multimodal analgesia in line with the ERAS protocol in colorectal surgeries is feasible, safe, and efficient as it yielded a promising result, which leads to effective pain control and quicker recovery, and aligns with global trends to minimise opioid use postoperatively.

## Declarations

### Ethics approval and consent to participate

Ethical approval was obtained from the Medical Research Ethics Committee, Ministry of Health Malaysia (Ethics approval number: 24-00484-KIQ). In view of the retrospective nature of this study that collected data from patient case notes without interaction with actual patients, informed consent was waived.

### Competing interests

None to declare.

### Funding

None to declare.

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# Appendix

## A. Data collection form

Version 2.0, dated 20/3/2024

**DATA COLLECTION FORM**
**MULTIMODAL ANALGESIA AS PART OF ENHANCED RECOVERY AFTER SURGERY (ERAS) IN COLORECTAL SURGERY**

**Assigned ID** :
**Diagnosis** :
**Age** :
**Performed Surgery** :
**Surgery Date** :

**Patient's demographic**

**ASA** : I / II / III / IV

**Comorbids** : Hypertension / DM / CKD / ESRF / IHD / Smoker / Obesity / Others:

_____

**BMI** : _____ kg/cm$^2$ **Weight** : _____ kg **Height** : _____ cm

**Pre-operative** (Sedative premedication should be avoided)
If given: _____ Reason:
_____

**Intra-operative**
**Anesthetic maintenance** : Desflurane + N2O / Desflurane + Air / TIVA / If others, state reason:

**Analgesia**

| | |
|---|---|
| IV Paracetamol | 1g / _____mg |
| IV Dexamethasone | 4mg/8mg |
| IVI Lignocaine | _____ mg / kg / H |
| IVI $MgSO_4$ | |
| IVI Ketamine | |
| IVI Dexmedetomidine | |
| TCI Remifentanil | |
| Epidural infusion | |
| Others | |
| Multilayer LA infiltration by surgeon : Yes / No | |

**Post-operative**

| **Analgesia** | | **Pain score** | **Recovery room** | **Ward** | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Arrival time: | **2H** | **6H** | **12H** | **POD1** | **POD2** |
| PCA | | | | | | | | |
| CWI | | At rest | | | | | | |
| Epidural | | At movement | | | | | | |
| Regional block | | ✱Rescue analgesia | | | | | | |
| Others | | **Level of activity** (1: sit up on bed ; 2: sit out of bed ; 3: sit out of bed >3H ; 4: ambulating with assistants) | | | | | | |
| **Oral analgesia** | | T. Paracetamol | | | | | | |
| | | T. Etoricoxib / T. Celecoxib | | | | | | |
| | | Others | | | | | | |

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