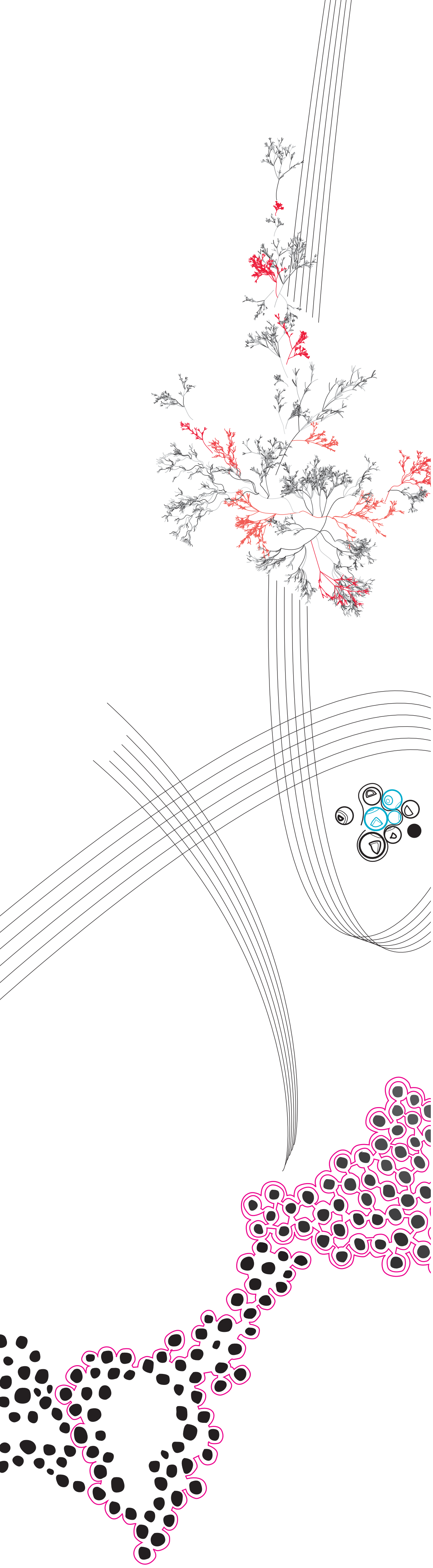

The impact of enhanced recovery on opioid intake after colorectal and small bowel surgery

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Contents

1 Abstract

Introduction In March 2020, Medisch Spectrum Twente (MST) introduced the Enhanced Recovery After Surgery (ERAS) protocol to enhance patient recovery with evidence-based interventions. This study investigates the impact of ERAS on daily in-hospital opioid use for four postoperative days of patients who underwent colorectal and/or small bowel surgery in MST compared to Pre-ERAS patients. Secondary objectives are identifying the most used type of opioids, assessing compliance of pain medication with the ERAS protocol and prescription practices, and exploring patient characteristics based on varying amounts of oxycodone intake.

Method The primary outcome of this retrospective cohort study was daily in-hospital opioid intake for four postoperative days between Pre-ERAS (surgery between February 2017 and January 2019) and ERAS (surgery between March 2020 and February 2023). Secondary outcomes included the most used opioid types, adherence to pain medication to the ERAS protocol and MST prescription practice, and characteristics related to varying levels of oxycodone intake. Data analysis involved multiple statistical tests, confounding factor identification, and multivariate logistic regression to calculate Odds Ratios (ORs).

Results The ERAS group had significantly lower odds of receiving opioids on days one, two, and three compared to the Pre-ERAS group. Corrected for confounding factors the ORs were respectively 0.18 (0.04 - 0.54 95%-CI), 0.31 (0.10 - 0.76 95%-CI) and 0.28 (0.09 - 0.70 95%-CI). For day zero, no significant difference was found. Short-acting oxycodone was the most administered postoperative opioid, with usage rates of 24.2%, 48.1%, 43.8%, and 37.6% for days zero, one, two, and, three, respectively. ERAS protocol adherence was highest on day zero (99.4%), but decreased on subsequent days: day one (41.8%), day two (80.0%), and day three (78.8%). The group with zero oxycodone intake (36.2% of patients) had a shorter length of stay (median of 2 days) compared to the High intake group (median of 5.5 days), with a p-value of 0.0002. They also reported lower VAS pain scores on days zero and one (medians of both 2) compared to the High intake group (medians of 2 and 4), with p-values of respectively 0.01 and 0.0001. Moreover, the Zero intake group had a quicker time until defecation (median of 1 night) compared to the High intake group (median of 2 nights), with a p-value of 0.01.

Conclusion The implementation of the ERAS protocol had a positive impact on in-hospital decrease of opioid intake on postoperative days one, two, and three. Short-acting oxycodone was the predominant opioid and zero oxycodone intake was associated with better patient outcomes such as a shorter LOS, lower VAS pain scores on day zero and one, and a shorter duration until defecation.

2 Introduction

In March 2020, Medisch Spectrum Twente (MST) implemented the Enhanced Recovery After Surgery (ERAS) program. This initiative was introduced by the Value Based Healthcare department of MST to improve outcomes, such as length of stay (LOS), that were deemed less optimal compared to other hospitals that had already implemented ERAS.

ERAS includes a set of evidence-based interventions that covers the entire patient care journey; the preoperative, intraoperative, and postoperative phases [1]. These interventions are designed with the primary goals to improve and speed up the recovery process of patients. ERAS includes interventions such as a short period without nutrition after surgery and early mobilization [2]. With the introduction of ERAS, there has been a shift in the standard approach to anaesthesia. Prior to ERAS, the standard practice involved epidural anaesthesia. However, the downside of epidural anaesthesia is that the epidural catheter typically stays in for an average of 48 hours [3]. This could affect the mobility of a patient during this period. In the ERAS protocol, the preferred approach is spinal anaesthesia, which remains effective for about 24 hours without the need for a catheter, promoting better postoperative mobility [4].

The decrease of opioid administration after surgery is another intervention of the ERAS protocol. Opioids are the strongest form of analgesics and are often part of a patient's pain medication. As pain can limit a patient's ability to move and participate in physical therapy or rehabilitation exercises, effective pain medication is especially important in the beginning of their recovery [5]. However, the use of opioids also has downsides. Opioids can have a negative influence on a patient's health, such as a decrease in bowel function, respiratory depression and less mobility due to sleepiness and dizziness [6]. The decrease of opioid administration is part of ERAS, but it was yet unclear whether the protocol was effective in opioid reduction in MST. This study focused primarily on colorectal and/or small bowel surgery, as ERAS was initially implemented for these procedures in MST. The primary research question was as follows: *What is the effect of the implementation of the Enhanced Recovery After Surgery protocol on opioid use per day for patients after colorectal and/or small bowel surgery during their hospital stay in Medisch Spectrum Twente, compared to opioid use for patients who underwent similar procedures before the implementation of ERAS?*
The secondary objectives included three key aspects of opioid administration within ERAS patients: identifying the most used postoperative type of opioid in MST during colorectal and/or small bowel surgery, assessing compliance of analgesic medication with the ERAS protocol, and exploring patient characteristics based on varying oxycodone intake levels, the only prescribed postoperative opioid in MST.

3 Research method

The data used in this study were collected from the ERAS Interactive Audit System (EIAS) database, specifically designed for the ERAS program [7]. This system records the usage of opioids on day zero (the day of surgery, after the surgical procedure) as well as on postoperative days one, two, and three. For the secondary objectives, administered medication data were extracted from the electronic health record, HiX, which was implemented in December 2021. The information recorded in EIAS and HiX was encrypted by data-analysts of the department of Value Based Healthcare of MST and therefore this research did not require informed consent of the patients or ethical approval according to the Dutch law. This was checked and confirmed by the Advisory Committee Medisch Spectrum Twente Enschede, the Netherlands.

3.1 Study Design and Patient Selection

For the primary and secondary research, a retrospective cohort study was conducted. The secondary research was exploratory.

Patients were eligible for inclusion in this research when they underwent elective laparoscopic or robotic, colorectal and/or small bowel surgery in MST, and were not readmitted after discharge. For the primary research question, two cohorts were used. The Pre-ERAS cohort was registered in EIAS as a reference group and is a random sample of patients who had surgery from February 2017 to January 2019. The second cohort consisted of patients after ERAS implementation, from March 2020 until February 2023. Unlike the Pre-ERAS cohort, this group was selected in its entirety, representing the ERAS cohort. For the secondary research, a subset of the ERAS cohort was used. Due to the implementation of HiX, only the ERAS patients registered between December 2021 and February 2023 were included.

3.2 Outcomes

The primary outcome focused on opioid intake, specifically whether a patient received postoperative opioids during their hospital stay for the first four postoperative days. The secondary outcomes aimed to explore the most administered type of opioids, the compliance of the administered pain medication with the ERAS protocol, along with characteristics related to varying levels of oxycodone use. Discrepancies were observed between the ERAS protocol and MST prescription practices. These differences can be seen in Table 1. Although the MST prescription practice deviated from the official protocol, it was applied within MST and therefore the compliance with the MST prescription practice was also researched. Excessive medication, for both adherence to the ERAS protocol and MST prescription practice, was defined as exceeding the recommended dosage.

Table 1: *Comparison of analgesic prescriptions between the ERAS protocol and the MST prescription practice for four postoperative days.*

	Day 0	**Day 1**	**Day 2**	**Day 3**
Metamizole 1000 mg				
ERAS Protocol	4	0	0	0
MST Prescription Practice	4	4	4	4
Short-acting oxycodone 5 mg				
ERAS Protocol	4	4	4	4
MST Prescription Practice	6	6	6	6
Paracetamol 1000 mg				
ERAS Protocol	4	4	4	4
MST Prescription Practice	4	4	4	4

Firstly, to explore the most administered type of opioids, opioids were categorized into Short-acting oxycodone, Long-acting oxycodone, Morphine, and Other (including tramadol, sufentanil, buprenorphine, fentanyl, methadone, pethidine, and piritramide). If patients used more than one type of opioid, they could fall into multiple categories. A note has to be made that morphine and

fentanyl, administered during both surgical and postoperative phases, were excluded from the day zero analysis. This exclusion was made because the phases could not be distinguished after data extraction.
Secondly, the analysis aimed to align administered analgesics with the ERAS protocol and MST prescription practice, as seen in Table 1. In the final secondary outcome analysis, patients were grouped based on cumulative daily oxycodone amounts: 0 mg daily throughout the entire stay (No intake), 0-20 mg daily throughout the entire stay (Low intake), one or more days with intake over 30 mg (High intake), and all patients not falling into the other categories, with on no day an intake surpassing 30 mg (Intermediate intake).

3.3 Variables

In the characteristics overview comparing Pre-ERAS and ERAS, the information was categorized into two main sections. The first main section covered patient characteristics which included age, gender, BMI (body-mass index), alcohol use (coded as non-alcohol for patients who stopped drinking prior to surgery), smoking (coded as non-smokers for patients who ceased smoking before surgery), recreational drugs, diabetes mellitus (controlled with medication or diet), and ASA-scores (American Society of Anaesthesiologists). The second main section focused on procedure characteristics containing laparoscopic surgery, main procedure, procedure length, no complications, non-serious (Clavien-Dindo gradients between I-IIIa) complications, and serious complications (Clavien-Dindo gradients between IIIb-V) [8]. Additionally, for the secondary outcome analysis, comparing different amounts of oxycodone intake, a new category was introduced: Peri/Post-hospital stay characteristics. These enclosed LOS, VAS (Visual Analogue Scale) pain and nausea scores for four postoperative days, metamizole (a Non-Steroidal Anti-Inflammatory Drug or NSAID) intake for four postoperative days, time until defecation, flatus, and solid food intake.

3.4 Statistical analysis

To compare opioid intake between Pre-ERAS and ERAS groups and investigate potential differences in various amounts of oxycodone intake, analyses were conducted in Rstudio version 4.2.1. Continuous data were presented as means (M) and standard deviations (SD), while dichotomous data were expressed as the number of people (N) and percentages (%). Non-normally distributed continuous data were represented using medians (Mdn) and interquartile ranges (IQR).

3.4.1 Primary outcome

For the continuous normally distributed data, an unpaired two-sided T-test was performed and for the non-normally distributed continuous data a Wilcoxon Rank Sum Test was performed [9]. For the categorical data, the statistical test was the Chi-squared test. To be statistically significant in this study, the p-value had to be lower than 0.05. The analysis to check for possible confounding consisted of the following steps:

1. Univariate logistic regression assessed the impact of ERAS on opioid use for each specific day.
2. All variables with $p < 0.15$ between the Pre-ERAS and ERAS cohorts were selected [10].
3. Selected variables were analyzed for their association with opioid use for each day, using the mentioned statistical tests. If a variable showed significance on one specific day, this was included in the multivariate analysis of each day to ensure equality.
4. Multivariate logistic regression was performed using the significant variables ($p < 0.15$) from the second and third steps.
5. No reduction of multivariate analysis was made to ensure consistency across all models.

3.4.2 Secondary outcomes

To analyze the four groups of varying oxycodone usage, the following tests were applied. For continuous normally distributed data, an ANOVA and for non-normally distributed data a Kruskal Wallis test was performed. For non-normally distributed countable data a Poisson regression was performed and for categorical data, the Chi-squared test [9].

4 Results

Figure 1 shows the patients selection, with an initial amount of 853 patients. Due to the selection criteria mentioned in Section 3.1, 413 patients were excluded and 440 patients were selected for the primary research question: 46 Pre-ERAS patients en 394 ERAS patients. For the secondary outcomes 231 patients were excluded from the 440 ERAS patients, since they were documented before the implementation of HiX, resulting in a subset of 163 ERAS patients.

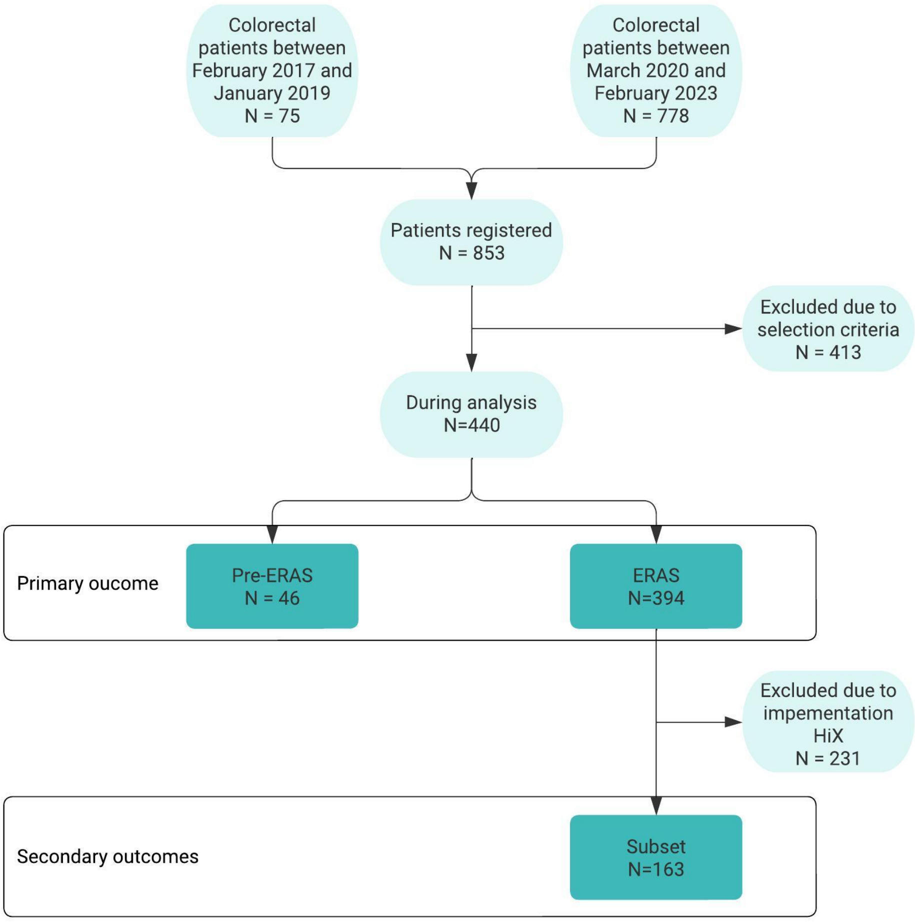

Figure 1: *A schematic overview of patient selection for primary and secondary outcomes.*

4.1 Characteristics

Characteristics are shown in Table 2, providing a detailed comparison between the Pre-ERAS and ERAS cohorts. Recreational drugs were used in 8.7% of the Pre-ERAS group compared to 1.8% in the ERAS group ($p = 0.01$). Differences in ASA-scores distribution were observed ($p = 0.0001$), with ASA 1 being more prevalent in Pre-ERAS (19.6%) than in ERAS (4.6%), while ASA 3 and ASA 4 occurred more often in the ERAS cohort compared to the Pre-ERAS cohort (35.3% and 2.8% versus 13.0% and 2.2%). The distribution of specific procedures also differed ($p = 0.03$), with hemicolectomy right and left and anterior resection of the rectum more common in Pre-ERAS, while sigmoid resection occured more frequently in ERAS. Stoma procedures did not occur in the Pre-ERAS cohort compared to 7.9% in the ERAS group.

Table 2: *Characteristics overview of Pre-ERAS and ERAS patients who underwent colorectal and/or small bowel surgery*

		Pre-ERAS N = 46	**ERAS N = 394**	**P-value**
Patient characteristics				
Age	*M*(SD)	66.9 (12.8)	65.5 (13.8)	0.48
Gender: Male	N (%)	27 (58.7)	183 (46.4)	0.12
BMI	*M*(SD)	26.9 (4.5)	26.5 (4.5)	0.55
Alcohol	N (%)	24 (52.2)	211 (53.6)	0.94
Smoker	N (%)	9 (19.6)	70 (17.8)	0.92
Recreational drugs	N (%)	4 (8.7)	7 (1.8)	0.01
Diabetes Mellitus	N (%)	8 (17.4)	52 (13.2)	0.58
ASA-score	N (%)			0.0001
ASA 1		9 (19.6)	18 (4.6)	
ASA 2		30 (65.2)	226 (57.4)	
ASA 3		6 (13.0)	139 (35.3)	
ASA 4		1 (2.2)	11 (2.8)	
Procedure characteristics				
Surgery: Laparoscopic	N (%)	45 (97.8)	372 (94.4)	0.53
Main procedure	N (%)			0.03
Hemicolectomy right		23 (50.0)	135 (34.3)	
Hemicolectomy left		2 (4.3)	31 (7.9)	
Sigmoid resection		5 (10.9)	89 (22.6)	
Ant. resect. rectum		9 (19.6)	70 (17.8)	
Stoma procedure		0 (0.0)	31 (7.9)	
Other		7 (15.2)	37 (9.4)	
Procedure length (min)	*M*(SD)	113.3 (52.2)	120.1 (56.1)	0.41
Complications	N (%)			1.00
No		41 (89.1)	330 (83.8)	
Non-serious		4 (8.7)	48 (12.2)	
Serious		1 (2.2)	16 (4.1)	

Abbreviations: BMI = Body Mass Index, ASA = American Society of Anaesthesiologists, Ant. resect. rectum = Anterior resection rectum.

4.2 Primary outcome

Table 3 shows the hospital occupancy for each day. There was a disparity in discharge patterns. Patients in the Pre-ERAS cohort began to be discharged on day three. In contrast, the ERAS group demonstrated earlier discharges with two patients leaving on day zero, six on day one, and 69 on day two. On day three, 112 patients from the ERAS group were discharged, while only three patients did so in the Pre-ERAS cohort.

Table 3 demonstrates that the Odds Ratios (ORs) for day one, two, and three show a significantly lower likelihood of administering opioids to ERAS patients compared to Pre-ERAS patients, with ORs of respectively 0.17 (0.04 - 0.48 95%-CI), 0.27 (0.09 - 0.64 95%-CI) and 0.22 (0.07 - 0.53 95%-CI). Gender, recreational drugs, ASA-scores, and main procedure demonstrated p-values <0.15, shown in Table 2, suggesting potential confounding. Subsequent confounding analysis identified gender, recreational drugs, and ASA-scores as confounding factors. After adjusting for these confounders, the ORs of day one, two, and three stayed relatively consistent, respectively 0.18 (0.04 - 0.54 95%-CI), 0.31 (0.10 - 0.76 95%-CI), and 0.28 (0.09 - 0.70 95%-CI). There was no significant difference on day zero. This holds true for both the uncorrected and corrected ORs.

Table 3: *Hospital occupancy, odds ratios, and their corresponding 95%-CI for opioid use between Pre-ERAS and ERAS patients*

	N*	No opioids	Opioids	OR	95%-CI	OR**	95%-CI**
Opioid use day 0							
Pre-ERAS	45***	2 (4.4%)	43 (95.6%)	0.68	0.11 - 2.40	0.80	0.12 - 2.97
ERAS	392	25 (6.4%)	367 (93.6%)				
Opioid use day 1							
Pre-ERAS	46	3 (6.5%)	43 (93.5%)	0.17	0.04 - 0.48	0.18	0.04 - 0.54
ERAS	386	112 (29.0%)	274 (71.0%)				
Opioid use day 2							
Pre-ERAS	46	5 (10.9%)	41 (89.1%)	0.27	0.09 - 0.64	0.31	0.10 - 0.76
ERAS	317	99 (31.2%)	218 (68.8%)				
Opioid use day 3							
Pre-ERAS	43	5 (11.6%)	38 (88.4%)	0.22	0.07 - 0.53	0.28	0.09 - 0.70
ERAS	205	77 (37.6%)	128 (62.4%)				

*Hospital occupancy fluctuates as patients were discharged.

**Corrected for gender, recreational drug use and ASA-scores.

***One patient was excluded from the analysis of this day due to an unknown value in opioid use.

4.3 Secondary outcomes

For the secondary outcomes a subset, as seen in Figure 1, containing 163 ERAS patients was used.

4.3.1 Type of opioids

Whether and which type of opioids were administered, are shown Table 4. The most used opioid on all days is short-acting oxycodone, with respectively 24.2%, 48.1%, 43.8%, and 37.6% for days zero, one, two, and three.

Table 4: *Different type of opioids administered to ERAS patients*

	N*	Any opioids used N(%)	Short-acting oxycodone N(%)	Long-acting oxycodone N(%)	Morphine N(%)	Other N(%)
Day 0	161	53 (32.9%)	39 (24.2%)	15 (9.3%)	- (-%)**	13 (8.1%)**
Day 1	158	78 (49.4%)	76 (48.1%)	13 (8.2%)	3 (1.9%)	1 (0.6%)
Day 2	128	60 (46.9%)	56 (43.8%)	18 (14.1%)	4 (3.1%)	3 (2.3%)
Day 3	85	36 (42.4%)	32 (37.6%)	13 (15.2%)	10 (11.2%)	1 (1.2%)

*Hospital occupancy fluctuates as patients were discharged.

**Due to exclusion of morphine and fentanyl for day zero in the dataset.

As mentioned in Section 3.2, patients could fall into multiple categories. Not shown in Table 4 is that patients can receive a combination of short-and long-acting oxycodone. For day zero this was one patient (0.6%). This increased to 12 (7.6%), 16 (12.5%), and 10 (11.2%) patients on days one, two, and three, respectively.

4.3.2 Compliance with protocol

To calculate the compliance with the ERAS protocol and the MSt prescription practice, the hospital occupancy for each day as shown in Table 4 were used. Table 5 shows that nearly all patients received pain medication according to the ERAS protocol on day zero. However, on day one, there was a shift in protocol compliance, since 57.6% of the patients received an excessive amount of metamizole, and 41.8% of the patients received analgesics according to the ERAS protocol.

Table 5: *Adherence to ERAS protocol*

	Within protocol	**Excessive oxycodone**	**Excessive paracetamol**	**Excessive metamizole**	**Excessive use of multiple analgesics**
Day 0	160 (99.4%)	0 (0.0%)	1 (0.6%)	0 (0.0%)	0 (0.0%)
Day 1	66 (41.8%)	7 (4.4%)	2 (1.3%)	91 (57.6%)	8 (5.1%)
Day 2	100 (80.0%)	6 (4.8%)	3 (2.4%)	23 (18.4%)	4 (3.2%)
Day 3	67 (78.8%)	3 (3.5%)	0 (0.0%)	15 (17.6%)	0 (0.0%)

Table 6 shows the compliance to the MST prescription practice, as shown in Table 1 in Section 3.2. Table 6 shows that the percentages of compliance to the MST prescription practice for days zero, one, two, and three were respectively, 99.4%, 95.6%, 96.1%, and 97.6%.

Table 6: *Adherence to MST prescription practice*

	Within practices	**Excessive oxycodone**	**Excessive paracetamol**	**Excessive metamizole**	**Excessive use of multiple analgesics**
Day 0	160 (99.4%)	0 (0.0%)	1 (0.6%)	0 (0.0%)	0 (0.0%)
Day 1	151 (95.6%)	1 (0.6%)	3 (1.9%)	4 (2.5%)	1 (0.6%)
Day 2	123 (96.1%)	1 (0.8%)	3 (2.3%)	2 (1.6%)	1 (0.8%)
Day 3	83 (97.6%)	1 (1.2%)	0 (0.0%)	1 (1.2%)	0 (0.0%)

4.3.3 Varying amounts of oxycodone intake

The final analysis showed that 130 patients (79.8%) used less than 20 mg of oxycodone per day (short-acting as well as long-acting oxycodone) during their entire hospital stay. From this group 59 patients (36.2%) had no oxycodone administered during their hospital stay. The association of varying oxycodone amounts on different characteristics, such as LOS and VAS pain scores, was researched, as shown in Table 7.

The Zero intake group had a significantly higher mean age of 69.0 years, compared to other groups (p = 0.04). ASA-scores also differed significantly, with more ASA 3 patients in the Zero intake group, compared to the other groups (p = 0.0001). Defecation time varied with a median of one night in the Zero intake group, to a median of two nights in the Low, Intermediate, and High intake groups (p = 0.02). Metamizole intake increased with the oxycodone intake, but it showed only a significant lower intake in the Zero intake group on day one compared to the other groups (p = 0.02). VAS pain scores showed a significant difference on days zero and one, with lower VAS pain scores in the Zero intake group compared to patients who received oxycodone (p-values of respectively 0.01 and 0.0001). Additionally, the LOS was significantly different between groups, with a median of 2 nights in the Zero intake group compared to medians of 3 , 4, and 5.5, for the Low, Intermediate, and High intake groups, respectively. Although not significant, the procedures anterior resection of rectum and stoma procedures occurred most often in the High intake group.

Table 7: *Characteristics overview of patients with zero, low, intermediate or high oxycodone intake*

		Zero intake N = 59	**Low intake N = 71**	**Intermediate intake N = 21**	**High intake N = 12**	**P-value**
Patient characteristics						
Age	*M*(SD)	69.0 (10.9)	66.8 (12.8)	54.7 (18.7)	55.3 (17.0)	0.04
Gender: Male	N (%)	25 (42.4)	29 (40.8)	9 (42.9)	6 (50.0)	0.95
BMI	*M*(SD)	26.5 (3.5)	26.2 (4.4)	26.5 (4.3)	25.2 (2.8)	0.57
Alcohol	N (%)	30 (50.8)	42 (59.2)	14 (66.7)	4 (33.3)	0.24
Smoker	N (%)	8 (13.6)	14 (19.7)	7 (33.3)	3 (25.0)	0.25
Recreational drugs	N (%)	0 (0.0)	2 (2.8)	1 (4.8)	0 (0.0)	0.44
Diabetes Mellitus	N (%)	10 (16.9)	7 (9.9)	2 (9.5)	0 (0.0)	0.08
ASA-score	N (%)					0.0001
ASA 1		2 (3.4)	7 (9.9)	0 (0.0)	0 (0.0)	
ASA 2		34 (57.7)	42 (59.2)	18 (85.7)	8 (66.7)	
ASA 3		23 (39.0)	22 (31.0)	3 (14.3)	3 (25.0)	
ASA 4		0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)	
Procedure characteristics						
Surgery: Laparoscopic	N (%)	55 (93.2)	65 (91.5)	20 (95.2)	10 (83.3)	0.64
Main procedure	N (%)					0.54
Hemicolectomy right		18 (30.5)	28 (39.4)	7 (33.3)	1 (8.3)	
Hemicolectomy left		3 (5.1)	6 (8.5)	3 (14.3)	2 (16.7)	
Sigmoid resection		14 (23.7)	14 (19.7)	4 (19.0)	2 (16.7)	
Ant. resect. rectum		11 (18.6)	13 (18.3)	3 (14.3)	3 (25.0)	
Stoma procedures		9 (15.3)	4 (5.6)	2 (9.5)	4 (33.3)	
Other		4 (6.8)	6 (8.5)	2 (9.5)	0 (0.0)	
Procedure length (min)	*M*(SD)	110.8 (54.1)	126.1 (52.9)	156.5 (108.6)	116.2 (98.0)	0.38
Complications	N (%)					0.56
No		54 (91.5)	59 (83.1)	20 (95.2)	9 (75.0)	
Non-serious		5 (8.5)	9 (12.5)	1 (4.8)	2 (16.7)	
Serious		0 (0.0)	3 (4.2)	0 (0.0)	1 (8.3)	
Peri/Post-hospital stay characteristics						
LOS	*Mdn*(IQR)	2 (1.5-3)	3 (2-4)	4 (3-6)	5.5 (4-8)	0.0002
VAS pain day 0	*Mdn*(IQR)	2 (1-2)	2 (1-3)	2 (2-3)	2 (2-4)	0.01
VAS pain day 1	*Mdn*(IQR)	2 (1-2)	2 (1-3)	3 (1-4)	4 (2.5-5.5)	0.0001
VAS pain day 2	*Mdn*(IQR)	1.7 (1-2)	2.4 (1-3)	2.5 (2-3)	2.8 (2-4)	0.25
VAS pain day 3	*Mdn*(IQR)	2 (2-2)	2 (1-4)	2 (2-3)	2 (2.5-4)	0.63
VAS nausea day 0	*Mdn*(IQR)	0 (0-2)	0 (0-0)	0 (0-1)	0 (0-0)	0.75
VAS nausea day 1	*Mdn*(IQR)	0 (0-2)	0 (0-1)	0.5 (0-1.3)	1.5 (0.8-2.3)	0.34
VAS nausea day 2	*Mdn*(IQR)	0.5 (0-2)	2 (0-3.8)	2 (0.3-4.5)	0 (0-0)	0.16
VAS nausea day 3	*Mdn*(IQR)	0 (0-2)	1 (0-3.8)	0 (0-1.5)	1.5 (0.3-3.5)	0.51
Metamizole day 0	N (%)	54 (91.5)	68 (95.8)	19 (90.5)	11 (91.7)	0.77
Metamizole day 1	N (%)	29 (49.2)	40 (56.3)	13 (61.9)	9 (75.0)	0.02
Metamizole day 2	N (%)	3 (5.1)	11 (15.5)	4 (19.0)	5 (41.7)	0.61
Metamizole day 3	N (%)	2 (3.4)	7 (9.9)	2 (9.5)	4 (33.3)	0.08
Defecation (nights)	*Mdn*(IQR)	1 (1-2)	2 (1-2)	2 (1-4)	2 (1-2)	0.01
Flatus (nights)	*Mdn*(IQR)	1 (1-1)	1 (0-1)	1 (1-2)	2 (1-2)	0.33
Solid food (nights)	*Mdn*(IQR)	0 (0-1)	0 (0-0)	0 (0-0)	0 (0-0)	0.74

Abbreviations: BMI = Body Mass Index, ASA = American Society of Anaesthesiologists, Ant. resect. rectum = Anterior resection rectum, LOS = Length of stay, VAS = Visual Analogue Scale.

5 Discussion

In this study, it was found that opioid usage on postoperative days one, two, and three in MST significantly decreased since the implementation of ERAS. Furthermore, short-acting oxycodone was the most administered postoperative opioid to ERAS patients. By examining different doses of oxycodone intake, notable differences were observed for several key factors. These key factors included a higher age, high ASA-scores, shorter LOS, lower VAS pain score on day zero and one, less usage of metamizole on day one, and a shorter duration until defecation in nights for the Zero intake group compared to various amounts of oxycodone intake.

Explanation of primary outcome

To the best of the researcher's knowledge, this retrospective observational data analysis stands as the first study to explore the effects of ERAS on all in-hospital postoperative used opioids for colorectal and/or small bowel surgery, comparing outcomes with a retrospective cohort of Pre-ERAS patients who underwent similar procedures. The analyses involved four seperate models. Patients in both cohorts received opioids on multiple days in the ERAS group, indicating an overlap of patients on different postoperative days. This approach provided an accurate representation of the hospital situation.

Liu et al. studied opioid use beyond 7, 30, 90, and 180 days in colorectal patients, which all showed a decrease after ERAS implementation [11]. George et al. and Edney et al. reported a consistent outcome, showing a reduction of in-hospital opioid use after the implementation of ERAS in paediatric colorectal surgery [12, 13]. Portinari et al. observed a significant reduction in postoperative intravenous opioid use in adults undergoing colorectal and small bowel surgery after the implementation of ERAS [14]. These findings collectively support the positive effects of enhanced recovery pathways after colorectal and/or small bowel surgery.

A discrepancy was observed between the complete ERAS dataset and the subset of the dataset. In the complete dataset, opioids were administered to at least 60.0% of the patients each day, while the subsets suggests that this percentage never surpassed 50.0% for each day. The differences in outcomes could result from a potential decline in opioid prescriptions over time, due to a more cautious prescribing approach.

Explanation of secondary outcomes

Zero oxycodone intake showed better patient outcomes, such as lower VAS pain scores and shorter LOS, compared to Low, Intermediate, and High oxycodone intake. No research was found for specifically oxycodone, but there are studies that show the same results based on general opioid intake. The decrease in LOS when using less opioids is also proved by the earlier mentioned articles of George and Edney [12, 13]. The relation between LOS and oxycodone intake suggests that as oxycodone intake increases, LOS also tends to increase, as supported by Barletta et al.'s research on opioids in general [6]. The direction of this relation, whether increased oxycodone leads to longer LOS or vice versa, remains unclear. Furthermore, multiple studies contradicted the finding that ASA 3 patients, after colorectal surgery, use fewer opioids and have a shorter LOS than patients with lower ASA-scores [15, 16]. While a comprehensive explanation is lacking, an analysis of the 13 ASA 3 patients not receiving oxycodone revealed a potential reason. Some patients received additional pain medication in the recovery, potentially reducing the need for further analgesics afterwards. For the remaining cases, it is possible that their severe systemic diseases, the reason for their ASA 3 classification, elevated their pain threshold, requiring less pain relief as they could tolerate pain more easily. The finding that opioid intake can lead to a longer time until defecation, aligned with previous studies [6, 17, 18]. However, it was observed that the Intermediate intake group had a median of 2 with an IQR of 1-4 nights, while the High intake group had a median of 2 and IQR of 1-2 nights. A potential explanation was found, as patients with High intake often receive more laxatives than patients in the Intermediate intake group, perhaps to prevent side effects of oxycodone.

Sarin et al. demonstrated the relation between implementation of ERAS and lower pain scores, even with a reduced intake of opioids [19]. This correlation aligns with the earlier discussed results. However, it is noteworthy that in this study the use of metamizole, an NSAID, increased with the oxycodone intake [14]. Usage of metamizole after day zero is against ERAS guidelines, which caution against the use of NSAIDs due to their potential to induce anastomotic leakage, even if there is still debate about this statement [2, 20, 21]. Besides the potential to induce anastomic leakage, one may question the administration of metamizole on only day zero at all. Given that spinal anaesthesia is still effective on day zero, the need for additional analgesics seems unlikely. On day one, when spinal anaesthesia has worn off, the use of extra analgesics becomes more plausible which is not the case in the ERAS protocol. Administering metamizole on multiple days, as done in MST, may be aimed at maintaining a consistent pain management level, which is more in line with effective pain management than administering it on day zero only.

Strengths and limitations

Prominent strengths of this study are the size of the dataset and the details of the dataset with regard to administered medication for ERAS patients. Additionally, the research shed light on discrepancies between the ERAS protocol and the MST prescription practice. The discrepancy in oxycodone prescriptions could be due toun awareness among prescribing specialists, while the inconsistency in metamizole administration, as mentioned previously, might stem from the need for effective pain management. In this study, a homogeneous group was selected by excluding cases of open surgery and readmissions. Also, all patients who did not undergo elective surgery were excluded. Readmitted patients were excluded because readmission could influence the need for analgesics. When including all patients, accounting for the same confounders, the odds ratios remained consistent, showing a significant difference for postoperative days one, two, and three.

Limitations of this study are the exclusion of morphine and fentanyl on day zero, which may introduce bias by overlooking postoperative administration. Further research could explore the characteristics of patients receiving additional morphine and fentanyl on day zero. The variation in discharge times between the Pre-ERAS and ERAS groups, add complexity to the analysis, limiting insights into the overall opioid use. The absence of home documentation results in a lack of insights into pain scores and opioid intake after discharge. However, MST is introducing a program where patients home monitor their analgesics after discharge, which makes further research on opioid intake possible [22].

Recommendations

Based on this study, three recommendations are made to further decrease postoperative opioid administration. Firstly, implementing opioid-free anaesthesia (OFA) provides a potential solution to decrease post-operative opioid use. J. Mulier, a Belgian anaesthesiologist, supports this argument with the concept of the opioid paradox [23]. This paradox suggests that peri-operative opioid administration leads to an increased need for post-operative opioids. The global rise of OFA involves replacing opioids with alternative drugs and techniques, such as a multimodal analgesics approach, demonstrating comparable outcomes in terms of complications and hospital stay duration [24, 25]. It is recommended that MST explores the possibilities of OFA in collaboration with their anaesthesiologists.

The second recommendation is to reduce opioid prescriptions. Although the implementation of ERAS successfully reduced opioid intake in MST, there is still room for improvement, especially considering the administration of other opioids alongside oxycodone. Reducing prescriptions leads to less administration of opioids. Recently MST introduced regional pain medication agreements for oxycodone. This limits patients to three on-demand doses of short-acting oxycodone (5 mg each) and two doses of long-acting oxycodone daily, for a maximum of 5 days [26]. While reducing short-acting oxycodone is positive, the use of long-acting oxycodone may be questionable, given its potential to exceed protocol limits of 20 mg per day.

Lastly, to reduce opioid intake, offering enhanced preoperative patient education could be considered, as seen in literature [27]. Educating patients on the health impact of opioids could lead to a more cautious opioid intake.

6 Conclusion

The present study showed that the implementation of the ERAS protocol had a positive impact on the decrease of in-hospital opioid use on days one, two, and three in patients who underwent elective laparoscopic or robotic colorectal and/or small bowel surgery. Short-acting oxycodone, aligned with the ERAS protocol, was the main administered opioid. Lower oxycodone intake correlated with improved outcomes, such as a shorter LOS, lower VAS pain scores on days zero and one, and shorter duration until defecation. Whether improved patient outcomes were due to reduced oxycodone intake or better patient conditions prior to surgery remains uncertain. Recommendations to decrease oxycodone administration in MST are to explore OFA options, reduce opioid prescriptions, and to enhance patient education on opioids and their effects on a patient's health.

References

[1] Javier Ripollés-Melchor, Ane Abad-Motos, Maurizio Cecconi, Rupert Pearse, Samir Jaber, Karem Slim, Nader Francis, Antonino Spinelli, Jean Joris, Orestis Ioannidis, et al. Association between use of enhanced recovery after surgery protocols and postoperative complications in colorectal surgery in europe: the europower international observational study, 2022.

[2] UO Gustafsson, MJ Scott, M Hubner, J Nygren, N Demartines, N Francis, TA Rockall, TM Young-Fadok, AG Hill, M Soop, et al. Guidelines for perioperative care in elective colorectal surgery: Enhanced recovery after surgery (eras®) society recommendations: 2018. *World journal of surgery*, 43:659–695, 2019.

[3] Suhail A Khan, Haseeb A Khokhar, ARH Nasr, Eleanor Carton, and Sherif El-Masry. Effect of epidural analgesia on bowel function in laparoscopic colorectal surgery: a systematic review and meta-analysis. *Surgical endoscopy*, 27:2581–2591, 2013.

[4] I Virlos, D Clements, J Beynon, V Ratnalikar, and U Khot. Short-term outcomes with intrathecal versus epidural analgesia in laparoscopic colorectal surgery. *Journal of British Surgery*, 97(9):1401–1406, 2010.

[5] Paul W Hodges and Rob J Smeets. Interaction between pain, movement, and physical activity: short-term benefits, long-term consequences, and targets for treatment. *The Clinical journal of pain*, 31(2):97–107, 2015.

[6] Jeffrey F Barletta. Clinical and economic burden of opioid use for postsurgical pain: focus on ventilatory impairment and ileus. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*, 32(9pt2):12S–18S, 2012.

[7] Olle Ljungqvist, Tonia Young-Fadok, and Nicolas Demartines. The history of enhanced recovery after surgery and the eras society. *Journal of Laparoendoscopic & Advanced Surgical Techniques*, 27(9):860–862, 2017.

[8] Shimpei Miyamoto, Junichi Nakao, Takuya Higashino, Seiichi Yoshimoto, Ryuichi Hayashi, and Minoru Sakuraba. Clavien–dindo classification for grading complications after total pharyngolaryngectomy and free jejunum transfer. *PLoS One*, 14(9):e0222570, 2019.

[9] Aviva Petrie and Caroline Sabin. *Medical statistics at a glance*. John Wiley & Sons, 2019.

[10] Zoran Bursac, C Heath Gauss, David Keith Williams, and David W Hosmer. Purposeful selection of variables in logistic regression. *Source code for biology and medicine*, 3(1):1–8, 2008.

[11] Vincent X Liu, Abigail Eaton, Derrick C Lee, Vivian M Reyes, Shirley S Paulson, Cynthia I Campbell, Andy L Avins, and Stephen M Parodi. Postoperative opioid use before and after enhanced recovery after surgery program implementation. *Annals of surgery*, 270(6):e69, 2019.

[12] Jessica A George, Andres J Gonzalez Salazar, Ahmer Irfan, Laura Prichett, Isam W Nasr, Alejandro V Garcia, Emily F Boss, and Eric B Jelin. Effect of implementing an enhanced recovery protocol for pediatric colorectal surgery on complication rate, length of stay, and opioid use in children. *Journal of pediatric surgery*, 57(7):1349–1353, 2022.

[13] John C Edney, Humphrey Lam, Mehul V Raval, Kurt F Heiss, and Thomas M Austin. Implementation of an enhanced recovery program in pediatric laparoscopic colorectal patients does not worsen analgesia despite reduced perioperative opioids: a retrospective, matched, non-inferiority study. *Regional anesthesia and pain medicine*, 44(1):123–129, 2019.

[14] Mattia Portinari, Simona Ascanelli, Simone Targa, Elisabete Maria Dos Santos Valgode, Barbara Bonvento, Emidia Vagnoni, Stefano Camerani, Marco Verri, Carlo Alberto Volta, and Carlo V Feo. Impact of a colorectal enhanced recovery program implementation on clinical outcomes and institutional costs: a prospective cohort study with retrospective control. *International Journal of Surgery*, 53:206–213, 2018.

[15] ERAS Compliance Group. The impact of enhanced recovery protocol compliance on elective colorectal cancer resection: results from an international registry. *Annals of surgery*, 261(6):1153–1159, 2015.

[16] Paul M Cavallaro, Adam C Fields, Ronald Bleday, Haytham Kaafarani, Yao Yao, Thomas D Sequist, Khawaja Fraz Ahmed, Marc Rubin, Rocco Ricciardi, and Liliana G Bordeianou. A multi-center analysis of cumulative inpatient opioid use in colorectal surgery patients. *The American Journal of Surgery*, 220(5):1160–1166, 2020.

[17] Andrea Kurz and Daniel I Sessler. Opioid-induced bowel dysfunction: pathophysiology and potential new therapies. *Drugs*, 63:649–671, 2003.

[18] Sangeeta R Mehendale and Chun-Su Yuan. Opioid-induced gastrointestinal dysfunction. *Digestive diseases*, 24(1-2):105–112, 2006.

[19] Ankit Sarin, Erik S Litonius, Ramana Naidu, C Spencer Yost, Madhulika G Varma, and Lee-lynn Chen. Successful implementation of an enhanced recovery after surgery program shortens length of stay and improves postoperative pain, and bowel and bladder function after colorectal surgery. *BMC anesthesiology*, 16:1–10, 2015.

[20] Aneel Bhangu, Prashant Singh, J Edward F Fitzgerald, Alistair Slesser, and Paris Tekkis. Postoperative nonsteroidal anti-inflammatory drugs and risk of anastomotic leak: meta-analysis of clinical and experimental studies. *World journal of surgery*, 38:2247–2257, 2014.

[21] Sylvester Paulasir, Christodoulos Kaoutzanis, Kathleen B Welch, James F Vandewarker, Greta Krapohl, Richard M Lampman, Michael G Franz, and Robert K Cleary. Nonsteroidal anti-inflammatory drugs: do they increase the risk of anastomotic leaks following colorectal operations? *Diseases of the Colon & Rectum*, 58(9):870–877, 2015.

[22] Medisch Spectrum Twente. Zorg bij jou: medisch servicecentrum voor- en door zorgprofessionals op landelijke schaal. https://www.mst.nl/p/zorg-bij-jou-medisch-servicecentrum-voor-en-door-zorgprofessionals-op-landelijke-schaal/: :text=Zorg2024. Accessed: 20-02-2024.

[23] J Mulier and M Dekock. Opioid free general anesthesia, a new paradigm?, 2017.

[24] Hélène Beloeil. Opioid-free anesthesia. *Best Practice & Research Clinical Anaesthesiology*, 33(3):353–360, 2019.

[25] Evan D Kharasch and J David Clark. Opioid-free anesthesia: time to regain our balance, 2021.

[26] Medisch Spectrum Twente. Regionale afspraken pijnmedicatie. https://www.onsmst.nl/regionale-afspraken-pijnmedicatie/, 2024. Accessed: 30-01-2024.

[27] Rhami Khorfan, Meagan L Shallcross, Benjamin Yu, Nicholas Sanchez, Shelby Parilla, Julia M Coughlin, Julie K Johnson, Karl Y Bilimoria, and Jonah J Stulberg. Preoperative patient education and patient preparedness are associated with less postoperative use of opioids. *Surgery*, 167(5):852–858, 2020.