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Cohort Study

Pharmacotherapeutic prophylaxis and post-operative outcomes within an Enhanced Recovery After Surgery (ERAS®) program: A randomized retrospective cohort study☆

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ABSTRACT

Background: Pharmacotherapy prophylaxis embedded in Enhanced Recovery After Surgery (ERAS®) protocols is largely unknown because data related to agent choice, dosing, timing, and duration of treatment currently are not collected in the ERAS Interactive Audit System (EIAS®). This exploratory retrospective randomized cohort study characterized pharmacologic regimens pertaining to prophylaxis of surgical site infections (SSI), venous thromboembolism (VTE), and post-operative nausea and vomiting (PONV).

Materials and methods: The records of 250 randomly-selected adult patients that underwent elective colorectal (CR) and gynecologic/oncology procedures (GO) at an ERAS® site in North America were abstracted using REDCap. In addition to descriptive statistics, bivariate associations between categorical variables were compared.

Results: Rates of SSI, VTE, & PONV were 3.3%, 1.1%, and 53.6%, respectively. Mean length of stay (LOS) for CR was 6.9 days and for GO, 3.5 days ($p < 0.001$). The most common antibiotic prophylaxis was one-time combination cefazolin 2 g and metronidazole 500 mg between 16 and 30 min preoperatively after chlorhexidine skin preparation. The most frequent VTE prophylaxis was tinzaparin 4500 units SC daily continued for at least 7 days after hospital discharge in oncology patients. PONV was related to longer LOS in both groups. Total morphine milligram equivalents (MME) was positively related to PONV and LOS in both CR & GO groups.

Conclusion: Guideline-consistent pharmacologic prophylaxis for SSI and VTE for both CR and GO patients was associated with low complication, LOS, and readmission rates. LOS in both groups was highly influenced by total MME, incidence of PONV and multi-modal anesthesia.

1. Introduction

Numerous recent studies have documented the positive impact of Enhanced Recovery After Surgery (ERAS®) programs on post-surgical clinical, economic, and patient-centered outcomes [1–8]. While improvements in the frequency and severity of post-operative complications (POC) coupled with reduced length of stay (LOS) have been achieved through bundled approaches to care management, data is now emerging on the effects of pharmacotherapy-related ERAS® elements on surgical outcomes, such as opioid reduction, fluid and ileus

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management, and antibiotic prophylaxis [9–17]. However, specific pharmacotherapy selection in terms of agents, dosing, multi-modal strategies, proximity to the surgical incision, and duration of treatment on any surgical outcome are unknown [18]. In addition, data about the factors that lead to a post-acute care (PAC) discharge delay are sparse. Development of a surgical site infection (SSI) [19], emergence of a venous thromboembolism (VTE) [20,21] or intractable post-operative nausea and vomiting (PONV) [22,23] are common reasons to postpone the patient's discharge [24,25]. Evidence indicates that over 50% of all hospital adverse events are preventable [26], and a major post-operative complication (POC) (i.e. grade III or above) occurs in at least 40% of all surgical patients [27]. Moreover, the rates of the above POCs in patients undergoing colorectal (CR) or gynecologic/oncology (GO) surgeries are estimated to be between 2 and 36% for SSI [25,28], between 0.7 and 13% for VTE [25,29], and between 30 and 80% for PONV [30,31], illustrating a wide variation in patient outcomes that may be due, in part, to sub-optimal pharmacotherapy. For example, multi-center studies have found that less than one-half of surgical patients have adequate VTE prophylaxis both in hospital and after discharge [32], especially in those with cancer [33].

This follow-up exploratory feasibility study of a retrospective ERAS® cohort of elective colorectal and gynecologic/oncology patients aims to characterize the use of pharmacotherapy prophylaxis against SSI, VTE, and PONV perioperatively within one ERAS® site. In addition, it will speculate on the utility of collecting additional data points for pharmacotherapy-intensive ERAS® elements.

2. Methods

The standardized data collection methodology of and experience with EIAS® is outlined elsewhere [3]. The present study continues the research strategy for ERAS®-related pharmacotherapy that was introduced in a prior report [18]. In addition, the methodology and data dictionary of the present study was described previously and modified through several iterations by all authors [34]. Data were collected using REDCap (version 5.9.13, 2020) [35] by a trained individual with knowledge of EIAS® and the healthcare records maintained at Tom Baker Cancer Centre and Foothills Medical Centre in Calgary, Alberta, Canada. A simple randomization algorithm (http://www.random.org) was used to select 250 patients (128 colorectal and 122 gynecologic/oncology) ≥18 years of age admitted for elective surgery between October 2019 and December 2020 for inclusion in the analysis. To detect a significant difference for the least common POC, VTE, with a 0.2 β and 80% power, a sample size of at least 243 patients was needed based on an estimated 4% and 1% VTE incidence in the population and cohort, respectively. An a priori p value ≤ 0.05 was used for statistical significance. The ERAS® program at these Alberta Health Services institutions was initiated in June 2013. The elective cases of these two surgical services were selected because they were among the first ERAS® Society protocols to be implemented at the site, and were known to encompass an adequate number of cases to detect differences associated with the least common post-operative complication, VTE. Pharmacotherapy for prophylaxis of these common POCs was selected because of the variety of agents that could be used as well as their potential impact on LOS and re-admission. While not often used in retrospective study design, randomization was employed to optimize sample size, minimize bias, increase rigor, and enable generalization of results. Descriptive statistics were used for frequency tabulations, χ^2 for cross tabulations of categorical variables, and linear and logistic regression was employed to measure associations for each procedure and ERAS® site between dependent (medication-related) and independent (outcome-related) variables. Categorical variables were presented as N (%), and continuous variables were presented as mean (±S.D.). Univariate analyses were conducted to evaluate for differences in baseline patient characteristics, operative characteristics, and postoperative outcomes between patients who received antibiotics, anti-coagulants, and anti-emetics prior to and after surgery. Outcomes included the frequency and severity of POCs as assessed using Clavien-Dindo classification, LOS, and 7- and 30-day readmission as recorded in EIAS®. All statistical analyses were conducted using IBM SPSS Statistics (version 27, 2020). This study was approved by the Institutional Review Boards for Human Subjects Research at Mercer University (H2009218) and the University of Calgary (HREBA.CC-20-0358), and has been reported in line with the STROCSS criteria [36]. This study is registered at Research Registry and was conducted in accordance with the Declaration of Helsinki (researchregistry7297).

3. Results

Patient demographic and procedural variables are listed in Table 1. A total of 250 random patients were included in the analysis, broken down by procedure (128 colorectal and 122 gynecologic/oncology). The mean age was 59.9 years (range: 18 to 92), and 44% in the CR group were female. The average body weight was 77.6 kg (range: 42–162 kg), and about 10% of patients had an admission eGRF below 60 mL/min/1.73 m^2. The most common Current Procedural Terminology (CPT) code was surgical procedures on the female genital system (48.8%), followed by

Table 1
Key demographic and procedural variables.

Variable	Total (%)	Colorectal (%)	Gynecological/ Oncology (%)	Significance
Age (years ± S.D.)	59.9 (±20.7)	60.3 (±15.6)	59.5 (±13.0)	0.685
Gender				
Female	178 (71.2)	56 (43.8)	122	
Male	72 (28.8)	72 (56.2)	0	
Weight (kg)	77.6 (±20.7)	77.9 (±18.2)	77.2 (±23.1)	0.798
eGFR (mL/min/ 1.73m^2)	86.1 (±20.9)	83.9 (±23.3)	88.4 (±17.9)	0.084
ASA status				0.517
I	19 (7.6)	5 (3.9)	14 (11.5)	
II	140 (56.0)	73 (57.0)	67 (54.9)	
III	88 (35.2)	47 (36.7)	41 (33.6)	
IV	3 (1.2)	3 (2.3)	0	
Cancer diagnosis	154 (61.6)	73 (57)	81 (66.4)	0.717
Type of procedure				
Laparoscopic	74 (29.6)	74 (57.8)	0	
Open	166 (6.4)	44 (34.4)	122 (100)	
Converted to open	10 (4)	10 (7.8)	0	
Type of intraoperative anesthesia (multiple types)				
Epidural	14 (5.6)	13	1	
General	248 (99.2)	126	122	
Continuous lidocaine infusion	23 (9.2)	15	8	
TAP block w/ long-acting LA	136 (54.4)	20	116	
Wound infiltration w/ non-liposomal bupivacaine/ epinephrine	94 (37.6)	90	4	
Mechanical bowel preparation (MBP) for colorectal procedures				
None	174 (69.6)	48 (37.5)	122 (100)	
Laxatives only		6 (4.7)		
Laxatives w/oral antibiotics		48 (37.5)		
Oral antibiotics only		26 (20.3)		

laparoscopic procedures on the intestines (31.6%), and incisional procedures on the intestines (20.8%). About 62% of total cases had a diagnosis of cancer, most of which did not receive neoadjuvant radiation or chemotherapy. About 2/3 of all patients underwent an open procedure. Older CR patients with open procedures had a significantly longer LOS than laparoscopic cases (9.1 v. 5.8 days; $p = 0.016$). All GO cases had open procedures.

Most patients (91.2%) were classified as American Society of Anesthesiologists (ASA) grade II or III, and almost all (99.2%) received general anesthesia with over one-half of CR cases (54.4%) receiving wound infiltration with non-liposomal bupivacaine and epinephrine. Transversus Abdominis Plane (TAP) block with non-liposomal bupivacaine and epinephrine combined with gaseous anesthesia was associated with a significantly lower LOS compared to all other anesthetic combinations in GO patients (4.18 v. 6.46 days; $p = 0.002$). Used only in CR cases, mechanical bowel preparation (MBP) with either laxatives or oral antibiotics (neomycin and metronidazole) or both was not associated with lower SSI, LOS, or re-admission rates. None of the differences between CR and GO groups were statistically significant.

Table 2 lists data abstracted from the EIAS® database. The most common POC grade was II, and 148 patients (59.2%) were reported to have at least 1 complication. A total of 8 patients had SSI (3.3%), 3 experienced a VTE (1.1%), and 137 patients had PONV (53.6%) as a POC. The mean LOS between the two surgical cohorts were significantly different (6.9 v. 3.5 days; $p < 0.001$). Four (1.6%) patients were re-admitted within 7 days, and 17 patients (6.8%) between 8- and 30-days post-discharge. CR patients had a higher rate of 30-day readmission. Patients in both groups that experienced PONV stayed 1 day longer in hospital, and patients that received only epidural anesthesia and haloperidol had significantly longer LOS.

For SSI prophylaxis, the most common intravenous antibiotic prophylaxis was combination cefazolin 2 g and metronidazole 500 mg (92.8%) between 16 and 30 min prior to surgical incision time (50.6%) (see Table 3). The typical duration of prophylaxis was one pre-operative dose (98.2%), and 5.6% received an intra-operative dose. All but one patient received topical skin antisepsis treatment, with the majority (96.4%) receiving chlorhexidine. Risk stratification scoring for infection was not used, and 5 in CR group and 3 in GO developed SSI, three of which were incisional. Table 3 lists the timing of parenteral antibiotic administered pre-operatively in relation to the surgical incision for SSI prophylaxis, illustrating that over 70% received antimicrobial prophylaxis within 30 min of incision.

For VTE prophylaxis, the most frequent regimen for both groups was compression stockings (98.8%), unfractionated heparin 5000 units SC (1 dose <6 h pre-operatively - 89.7%), with tinzaparin 4500 units SC daily (94%) given post-operatively in hospital (99.2%) and continued at home (54.8%). Patients with tinzaparin at home (n = 133) received it for at least 7 days, and dose adjustments based on patient weight occurred in 22 patients (9.8%). Patients with a cancer diagnosis received anti-thrombosis prophylaxis in 86.3% of cases. Risk stratification scoring for VTE was not used, and VTEs occurred in a peripheral limb (2) and the lung (1).

Table 4 details PONV prophylaxis. The most frequently administered pre-induction anti-emetic was aprepitant combined with dexamethasone. Ondansetron, dexamethasone, and haloperidol were often given together at extubation. PONV was related to longer LOS in both CR (8.0 v.5.2 d; $p = 0.015$) & GO patients (4.5 v.2.5 d; $p = 0.01$). Apfel risk stratification scoring for PONV was used in 90.4% of cases, and 57.4% of all patients received >7 anti-emetic doses post-operatively (without specifying around the clock or as needed dosing). Of note, all GO patients received metoclopramide every 6 h for 48 h post-operatively. Only aprepitant use was associated with a lower LOS in GO (6.33 v. 3.1 days; $p = 0.017$) but not CR patients (7.23 v. 5.36 days; $p = 0.214$).

Table 5 illustrates the use of opioid narcotics converted to MME and its impact on PONV. More total morphine milligram equivalents (MME) was given in CR (146.5 ± 226.1 mg) than GO (73.8 ± 268.5 mg; $p = 0.021$). Total MME was significantly related to incidence of PONV and LOS duration in both groups. In addition, CR patients had a significantly higher incidence of PONV and higher MME than GO patients. Based on the results of this analysis, a pattern emerged related to regimen characteristics (selection, dosing, timing in proximity to incision, and duration of treatment) and their relationship to the frequency/severity of POCs and LOS for SSI and VTE prophylaxis. Administration of cefazolin at a protocolized 2-g dose combined with metronidazole 500 mg given intravenously within 16–30 min of incision after chlorhexidine skin preparation was associated with a low SSI rate. Use of MBP with laxatives and/or oral antibiotics in CR cases (not used in GO cases) was not associated with a lower incidence of SSI or LOS. Pre-operative SC heparin and use of tinzaparin SC initiated 12 h after incision combined with compression stockings was associated with a low VTE complication rate. However, there were no meaningful pharmacological alternatives used at the site to prevent either of these complications that would allow comparisons of associated POCs or LOS.

Table 2
Patient outcome variables.

Variable	Total (%)	Colorectal (%)	Gynecologic/ Oncology (%)	Significance
Complication				
Surgical site infection	8 (3.3)	5 (3.9)	3 (2.5)	n.s.
Venous thromboembolism	3 (1.1)	2 (1.6)	1 (0.8)	n.s.
Post-operative nausea & vomiting	137 (53.6)	78 (60.9)	59 (48.4)	<0.001
Mean length of hospital stay (days)	5.2	6.9	3.5	<0.001
With PONV		8.0	4.5	0.01
Without PONV		5.2	2.5	0.01
With epidural anesthesia only	9.4			
7-day readmission	4 (1.6)	2	2	0.323
30-day readmission	17 (6.8)	15	2	0.002

Table 3
Timing of surgical site prophylaxis with intravenous cefazolin and metronidazole.

Variable	Total (%)
Time of antibiotic administration	
Unknown	17 (6.8)
0–15 min prior	51 (20.5)
16–30 min prior	126 (50.6)
31–45 min prior	51 (20.5)
46–60 min prior	3 (1.2)
>60 min prior	1 (0.4)

Table 4
PONV prophylaxis and related agents.

Variable	Total (%)
Anti-emetic prior to induction	
aprepitant	132 (53.9)
dexamethasone	86 (35.1)
haloperidol	11 (4.5)
metoclopramide	14 (5.7)
ondansetron	13 (5.3)
Anti-emetic prior to extubation	
dexamethasone	91 (37.1)
granisetron	2 (0.8)
haloperidol	61 (24.9)
metoclopramide	5 (2.0)
ondansetron	172 (70.2)
neostigmine reversal	201 (80.4)
ketamine bolus	30 (12.0)

Table 5
Morphine milligram equivalents (MME) and PONV.

Variable	Colorectal	Gynecologic/ Oncology	Significance
Total MME in hospital (mg)	146.5 (±226.1)	73.8 (±268.5)	0.021
PONV present	256.6 (±270.3)	133.7 (±275.4)	0.026
PONV absent	116.3 (±146.0)	104.8 (±269.7)	0.559
Number of patients with PONV (%)	78 (60.9)	59 (48.4)	

4. Discussion

To our knowledge, this is the first study to characterize the selection of pharmacotherapy for prophylaxis of three common post-surgical complications - SSI, VTE, and PONV - within a cohort of colorectal and gynecologic/oncology surgical patients treated at an ERAS® site.

While not a primary purpose of the study, comparison of CR and GO patients revealed several pertinent findings. Significant differences between CR and GO patients for SSI and VTE were not found because very similar regimens were used. However, CR patients had a longer length of stay and a higher 30-day re-admission rate, which may be related more to the nature of the surgery. In addition, CR patients had almost twice as much total MME administered as GO patients, which may be explained by the higher LOS in CR patients. Average daily MME administration per patient was not different between CR and GO patients.

PONV as a complication was expected to be higher than SSI or VTE. Although the Apfel risk scoring system for prevention of PONV was used in most cases, prophylaxis did not prevent PONV in over half of the cases at some point during hospitalization. The impact of total MME on PONV and LOS was significant, with PONV incidence often doubling LOS. While these results for PONV incidence are lower than the 70 to 80% range often reported in the literature [23], anti-emetic regimen in high-risk patients might be improved through the use of additional agents with different mechanisms of action. These might include transdermal scopolamine, an anti-cholinergic, applied behind the ear pre-operatively and left on the skin post-operatively and a reduction in neostigmine use for neuromuscular blocker (NMB) reversal post-operatively in addition to aprepitant, dexamethasone, and ondansetron [37,38].

Another gap in the PONV data is whether around the clock (ATC) versus as needed (PRN) regimens were employed and at what point(s) in the hospital stay that PONV occurred. Aprepitant combined with at least two more anti-emetics in high-risk patients might provide better coverage to reduce PONV. In addition, routine use of multi-modal anesthesia that includes TAP blocks and pain management with reduced opioid exposure may reduce PONV and LOS in both groups. A fuller characterization of the pharmacotherapy of PONV may be warranted in future studies.

This study has several limitations and potential confounders, especially that it utilized data from patient encounters treated during the COVID pandemic. It is possible that only the most urgent elective cases were admitted for a surgical procedure during this time, and less urgent cases were deferred. In addition, data were collected at an ERAS®-experienced single center, and results may not be indicative of other ERAS® or non-ERAS® sites. No data was collected on longer term outcomes or for other factors known to affect LOS, such as early ambulation and feeding, no anxiolytics, among others.

An overarching purpose of this study was to determine whether any regimens of choice could be identified that would justify increasing the level of detail for pharmacotherapy in terms of agents, dose, frequency, and duration of therapy. Without adequate comparators from like institutions, recommendations for any guideline modification are premature, and caution should be used in making inferences to other settings. However, it is apparent that, in a real-world setting, the use of appropriately-timed and dosed combination cefazolin/metronidazole to prevent SSI and compression stockings combined with tinzaparin for VTE prophylaxis were significantly associated with at least one-half of the rates of these common POCs as compared to other literature reports, which occur in as high as 20% of cases.

No data was collected on longer term (>30 day) outcomes. Compliance rates with ERAS® protocol elements are known to affect post-surgical outcomes, but was not collected. Full compliance has been reported to be >90% of elements, between 70 and 90% is high compliance, and <70% low compliance. In some reports, ≥ 80% compliance was related to significantly lower POC, LOS, and re-admission rates [39]. Recently, province-wide compliance for CR and GO patients in Alberta was 67% and 75%, respectively [40]. Moreover, information about the incidence of post-operative ileus (POI) was not collected in this study. POI is best prevented through avoidance of both preoperative fasting and MBP, as well as use of opioid-sparing anesthesia and analgesia. POI cannot be ruled out as a contributor to PONV, especially in CR patients in this cohort that received MBP and had high total MME. The actual timing and dosing for aprepitant was missing from the record, and whether the PONV prophylaxis was administered ATC or PRN post-operatively was not collected. Propofol use, known to have direct anti-emetic effects, was not collected. No data were collected about nutritional factors, such as the patient's nutritional status or use of perioperative oral nutritional supplementation (ONS), in either group. These factors are known to affect patient comfort (especially nausea), insulin resistance, and LOS, since a "diet as tolerated" (DAT) assessment is needed for discharge. Recording ONS on the Medication Administration Record or a separate Nutrition Administration Record may facilitate POI reduction, early post-operative enteral feeding, and DAT evaluation [41]. Finally, a recent report provides a useful conceptual framework for studying the relationships of core elements bundled in ERAS colorectal programs based on variations in the primary outcomes of three sub-populations [42].

5. Conclusions

Use of guideline-consistent prophylaxis for SSI and VTE was associated with low POCs, LOS, and readmission rates. While pre-operative PONV risk was assessed routinely, selection of preventative agents was more variable and multi-factorial. LOS in both groups was highly influenced by total MME, incidence of PONV, and multi-modal anesthesia. Seven-day re-admission rate was low in both groups, and more men were re-admitted within 30 days. Research at additional ERAS® sites is needed to validate these findings and identify optimal multi-modal PONV prophylaxis regimens.

Ethical approval

This study was approved by the Institutional Review Boards for Human Subjects Research at Mercer University (H2009218) and the University of Calgary (HREBA.CC-20-0358).

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Author contribution

Author contributions: Conceived the project, Richard H. Parrish II (RHP) and Gregg Nelson (GN); drafted the data collection instrument, RHP; collected data, Rachelle Findley (RF); managed the REDCap database, RHP; wrote the first draft, RHP; edited all subsequent drafts, RHP, GN, RF, Kevin M. Elias (KE), Brian Kramer (BK), Eric G. Johnson (EJ), and Leah Gramlich (LG); and compiled the descriptive statistics RHP; reviewed the data collection instrument, RHP, GN, RF, BR, EJ, and

LG; reviewed statistical analysis and edited all subsequent drafts, all authors.

Research registration Unique Identifying number (UIN)

1. Name of the registry: This study is registered at Research Registry
2. Unique Identifying number or registration ID: researchregistry7297
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): https://www.researchregistry.com/browse-the-registry#home/registrationdetails/6176ffdf47d34d0021b030ac/

Guarantor

Richard Henry Parrish II.

Informed consent

Institutional review Boards at Mercer University and the University of Calgary deemed this study to be exempt from further review. Therefore, informed consent was not required.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Declaration of competing interest

No conflicts to disclose.

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Appendix A. Supplementary data

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