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Research Paper

A novel enhanced recovery protocol, combining multimodal analgesia with liposomal bupivacaine and pharmacologic intervention, reduces parenteral opioid use and hospital length of stay after colectomy – A cohort study

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ABSTRACT

Background: The objective was to evaluate the impact of a focused enhanced recovery protocol (ERP), which included multimodal analgesia with liposomal bupivacaine and targeted pharmacologic intervention with intravenous ketoroloac and metoclopramide, on postoperative parenteral opioids use (PPO) and length of hospital stay (LOS) after elective colectomy.

Methods: The study was a before-after and non-randomized control trial. 109 consecutive patients undergoing elective colectomy were divided into three cohorts: group 1 (n = 39): patients from surgical team 1 implementing ERP; group 2 (n = 34): time-matched controls from team 2 not using ERP; group 3 (n = 36): historical controls from team 1 before introduction of ERP. Cases for the three groups were reviewed by gender, age, ASA class, diagnosis, right or left colectomy, laparoscopic or open technique.

Results: Mean overnight PPO use in mg of hydromorphone analgesic equivalents was: 1.78 in group 1, vs 5.15 in group 2 ($p < 0.0001$), vs 4.36 in group 3 ($p = 0.0006$). Mean total PPO use was 2.69 in group 1, vs 16.17 in group 2 ($p < 0.0001$), vs 10.30 in group 3 ($p = 0.0017$). Mean LOS in days for group 1 was 2.31 (lap = 2.11, open = 2.82), vs 6.32 for group 2 (lap = 4.38, open = 7.52) ($p < 0.0001$), vs 4.08 for group 3 (lap = 3.38, open = 5.06) ($p < 0.0001$). There were 2 ileus cases in group 1 (5.3%), 7 in group 2 (20.6%), and 5 in group 3 (13.9%).

Conclusions: A novel ERP, using long-acting local anesthesia with liposomal bupivacaine and pharmacologic intervention, proved feasible and effective in reducing PPO, ileus and LOS in elective colectomy cases.

1. Introduction

Over the past fifteen years, numerous initiatives aimed at reducing hospital length of stay after elective colon resections have been proposed [1]. The main value of ERAS (enhanced recovery after surgery) or ERP (enhanced recovery protocol) pathways lies in minimizing disability to patients and reducing health care costs, without compromising safety. The term ERP appears preferable, since it also includes the multiple steps that should be implemented before surgery (e.g. “strong for surgery”, “prehabilitation”). The number of interventions proposed to achieve a hospital length of stay (LOS) reduction has varied significantly in the literature, while the ERP concept was being applied to other areas of surgery as well (e.g. upper gastrointestinal, urology, orthopedics, thoracic) [2]. Some ERP initiatives entail additional management costs, limiting their financial value [3]. In addition, some pathways are so complex, with so many separate interventions, that compliance has proven suboptimal (60–80%), and the contribution of each individual step to the overall outcome difficult to determine [4]. Other ERP initiatives have focused on new technology, such as robotic techniques, with a reported reduction from 6 to 5 days average LOS after colectomy, when compared to laparoscopic approach [5–7]. Finally, any initiative aimed at LOS reduction needs to be comparably effective in minimizing incidence of readmission to the hospital, which would negate any benefit [8–10].

In our investigation, we chose to focus on prevention of postoperative ileus, a major cause of prolonged hospital stay after colectomy, and its association with postoperative parenteral opioid

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(PPO) use in pain management [11,12]. Our initiative aimed at reducing PPO use by adding multimodal analgesia, including long-acting local anesthetics and intravenous ketorolac as a parenteral non-steroidal anti-inflammatory agent, proven safe and effective in previously published studies [13,14]. Additionally, we added intravenous metoclopramide, as a prokinetic agents, to promote early return of bowel function and reduce the incidence of post-operative paralytic ileus. We sought to evaluate the feasibility, efficacy and safety of a novel ERP for elective colectomy and its impact on PPO use and hospital LOS.

2. Methods

The investigation was a before and after, non-randomized cohort study. This work has been reported in line with the STROCSS criteria [15]. It included a retrospective review of an existing database and a prospective data collection into the same database (Epic Systems). The setting was a single general hospital, with consistent care teams. The study included 109 consecutive elective colectomy cases, both laparoscopic and open, divided into three groups. The demographics and main management differences for each group are reported in Table 1.

Group 1 patients were enrolled in the novel ERP. Preoperative education was implemented with patients/families, anesthesia, nursing and advance practice providers (APP) staff. Patients received selective mechanical bowel preparation (omitted for right colon procedures), with oral antibiotics (neomycin sulfate and metronidazole) the day before their operation. At the end of each operative case, the wound layers with parietal innervation (dermis, muscle fascia and parietal peritoneum) were infiltrated with a solution of liposomal bupivacaine (Exparel®), according to the technique described by Joshi et al. [15]. More specifically, 20 ml of bupivacaine liposome was mixed with from 10 to 30 ml of 0.25% bupivacaine with epinephrine 1:200,000, depending on the length of the incisions. Postoperative pain was managed initially with intravenous ketorolac (15 mg every 6 h as needed), while reserving hydromorphone or morphine use only to control severe pain, not adequately relieved with the above protocol. Intravenous metoclopramide (10 mg every 6 h) was routinely used postoperatively to minimize postoperative ileus and promote early return of bowel function.

Group 2 patients comprised the time-matched control cohort, treated by different surgical staff that did not utilize the ERP, but practiced in the same institution with the same anesthesia and nursing staff. These patients had routine mechanical bowel preparation the day before their operation, and did not receive Exparel®. They received PPO as first choice as needed via intravenous injection or PCA pump, then transitioned to intravenous NSAIDS as tolerated. They were given metoclopramide only as needed after occurrence of signs and symptoms of postoperative ileus (e.g. abdominal distention, nausea, vomiting).

Group 3 patients were the historical control cohort, treated by the same surgical team as group 1, prior to implementation of the novel ERP. They had selective bowel preparation and oral antibiotics, as in group 1, the day before their operation. They did not receive Exparel®. They received PPO as first choice as needed via intravenous injection or PCA pump, then transitioned to intravenous NSAIDS as tolerated. They were given metoclopramide only as needed for evidence of postoperative ileus. The purpose of evaluating group 3, in addition to group 2, was to assess the impact of the novel ERP on patients managed by a team that was otherwise consistent with group 1 in all other aspects of care delivery, including surgical technique.

No patient in the entire study received pre-operative oral gabapentin or celecoxib, intravenous steroids, NSAIDS, or alvimopan (Entereg®). All patients in the three groups received short-term (under 24 h) peri-operative intravenous antibiotic prophylaxis. Postoperative ERP steps were implemented after assessment of progression of care and lack of complications multiple times a day. Four discharge criteria were applied to all patients: evidence of return of bowel function (i.e. flatus or stool), ability to tolerate solid food by mouth, adequate pain control with oral medications, and safe placement of agreeable patient after discharge from the hospital (e.g. home, with or without visiting nurse care, or short-term rehabilitation facility).

Data was collected on age, gender and ASA class for each of the three groups. The diagnosis of “tumor” included both benign (endoscopically unresectable) and malignant neoplasms. The colectomy site was defined as “right” when it included an ileo-colonic anastomosis (e.g.: right colectomy, extended right colectomy). The colectomy was defined as “left” when it involved a colo-colonic or colorectal anastomosis (e.g. left colectomy, sigmoid colectomy, colostomy closure). In group 2 there were two robotic cases, that were included in the laparoscopic group. A case started laparoscopically that was converted to open, was classified as “open” in our analysis.

Main outcome measures were postoperative parenteral opioids use (PPO) in hydromorphone analgesic equivalents (10 mg morphine = 1.5 mg hydromorphone), both overnight and overall during hospitalization, and hospital LOS in days. The overnight PPO use was measured in order to assess immediate analgesic requirements upon awakening from general anesthesia and limit potential bias of a greater PPO use mostly influenced by a longer LOS.

Additional recorded data were complete avoidance of PPO, hospital LOS by surgical technique (laparoscopic versus open), incidence of postoperative ileus, and “ambulatory” cases (hospital LOS under 24 h with overnight stay).

None of the authors had any financial interest or conflict of interest with any industry, device, product or medication used in this study.

Statistical analysis of our data was done using R-software, version 3.2.2. Treatment effects were defined as the difference in the average of each outcome variable between units assigned to group 1 and units assigned to group 2 or 3, with comparisons of group 1 versus group 2, and group 1 versus group 3 conducted separately. Multivariate analysis was done using ANOVA, Student's *t*-test, and ordinary least squares (OLS) regression models with additive covariates. Normally distributed data were presented as means (standard deviation) or, for smaller sample sizes, as means (range), and categorical data as frequencies (percent). All statistical tests were two-sided and aimed to assess the plausibility of the null hypothesis that the average treatment effect is zero, with $\alpha = 0.05$ indicating statistical significance.

Table 1
Patients characteristics and management in the three cohorts.

	Group 1 (n = 39)	Group 2 (n = 34)	Group 3 (n = 36)
Mean Age in years (range)	66.7 (44–88)	60.7 (28–91)	62.3 (37–89)
Gender (M/F)	21/18	13/21	13/23
Mean ASA class	2.51	2.38	2.58
Diagnosis (tumor/other)	22/17	7/27	20/16
Site (Right/Left)	17/22	7/27	15/21
Technique (Lap/Open)	28/11	13/21	21/15
Liposomal Bupivacaine	YES	NO	NO
Metoclopramide	YES	PRN	PRN
PCA narcotics	NO	YES	YES
IV Opioids	2nd choice	1st choice	1st choice
Ketorolac	1st choice	2nd choice	2nd choice