Liposome bupivacaine (EXPAREL®) for extended pain relief in patients undergoing ileostomy reversal at a single institution with a fast-track discharge protocol: an IMPROVE Phase IV health economics trial

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Background: Postoperative opioid use following ileostomy reversal procedures contributes to postoperative ileus. We assessed the impact of a liposome bupivacaine-based, opioid-sparing multimodal analgesia regimen versus a standard opioid-based analgesia regimen on postsurgical opioid use. We also assessed health economic outcomes in patients undergoing ileostomy reversal at our institution, which employs an enhanced recovery discharge protocol.

Methods: In this single-center, open-label study, patients undergoing ileostomy reversal received postsurgical pain therapy via multimodal analgesia that included a single intraoperative administration of liposome bupivacaine or opioid-based patient-controlled analgesia (PCA) with intravenous morphine or hydromorphone. Rescue analgesia (intravenous [IV] opioids and/or oral opioid + acetaminophen) was available to all patients. Primary efficacy measures included postsurgical opioid use, hospital length of stay (LOS), and hospitalization costs. Secondary measures included: time to first rescue opioid use; patient satisfaction with analgesia; additional medical intervention; and opioid-related adverse events.

Results: Forty-three patients were enrolled and met eligibility criteria (IV opioid PCA group = 20; liposome bupivacaine-based multimodal analgesia group = 23). Postsurgical opioid use was significantly less in the multimodal analgesia group compared with the IV opioid PCA group (mean [standard deviation]: 38 mg [46 mg] versus 68 mg [47 mg]; \( P = 0.004 \)). Postsurgical LOS between-group differences (median: 3.0 days versus 3.8 days) and geometric mean hospitalization costs (US $6,611 versus US$6,790) favored the multimodal analgesic group but did not achieve statistical significance. Median time to first opioid use was 1.1 hours versus 0.7 hours in the multimodal analgesia and IV opioid PCA groups, respectively; \( P = 0.035 \). Two patients in the multimodal analgesia group and one in the IV opioid PCA group experienced opioid-related adverse events.

Conclusion: A liposome bupivacaine-based multimodal analgesic regimen reduced postoperative opioid consumption in patients undergoing ileostomy reversal under a fast-track discharge protocol. A reduction of 21% in LOS (0.8 days) was noted which, although not statistically significant, may be considered clinically meaningful given the already aggressive fast-track discharge program.

Keywords: surgery, ileostomy, multimodal analgesia, opioid-related adverse events, hospitalization cost, length of stay

Introduction
The rates of major and minor postoperative complications following ileostomy reversal procedures are reported to range between 22% and 33%.\(^1\)\(^6\) The incidence of small
bowel obstruction or postoperative ileus following ileostomy reversal may be as high as 12%.
Further, a meta-analysis of 48 ileostomy reversal studies found that 7.2% of patients
experienced bowel obstruction, more than one-third of whom (2.5%) required surgical intervention. Postoperative opioid use has been clearly identified as a predictor of gastrointestinal (GI) motility problems following abdominal surgery. 

The overall length of hospital stay (LOS) for patients undergoing ileostomy reversal varies widely in published reports; typical durations range between 4 days and 10 days. In recent years, there has been a trend toward use of enhanced or “fast-track” discharge protocols to reduce LOS in patients undergoing this procedure, predicated primarily on reducing the time to achieve tolerance of oral liquid/food intake and improved GI function.

Recently, liposome bupivacaine (EXPAREL®; Pacira Pharmaceuticals, Inc, Parsippany, NJ, USA), a long-acting liposomal formulation of bupivacaine, has been made available for postsurgical analgesia. Liposome bupivacaine is indicated for administration into surgical sites to produce postsurgical analgesia. Clinical studies across a range of surgical settings demonstrated that a single intraoperative administration of liposome bupivacaine was well tolerated and provided postsurgical analgesia for up to 72 hours. These studies also showed that liposome bupivacaine extended the time to first opioid use and reduced per-patient opioid use overall.

In the first published study from an ongoing series of liposome bupivacaine evaluations (designated IMPROVE, for Extended PaIn Relief Trial Utilizing the Infiltration of a Long-Acting Multivesicular LiPosome FoRmulation Of BupiVacaine, EXPAREL®), liposome bupivacaine, as part of a multimodal analgesic regimen, was compared with opioid-based patient-controlled analgesia (PCA) in patients undergoing open colectomy. This open-label, single-center study demonstrated that liposome bupivacaine-based multimodal analgesia led to significant reductions in hospital LOS, total cost of hospitalization, and postsurgical opioid use when compared with opioid-based PCA.

The current study, part of the IMPROVE series, was a comparison of liposome bupivacaine-based multimodal analgesia with opioid-based PCA, with respect to total opioid burden and health economic outcomes in adult patients undergoing ileostomy reversal at an institution that already had an aggressive patient discharge protocol.

Methods
This was a Phase IV, prospective, single-center, open-label, sequential study designed to evaluate the efficacy, safety, and health economic outcomes associated with a multimodal analgesia regimen including intraoperatively administered liposome bupivacaine 266 mg compared with postsurgical PCA with intravenously (IV) administered morphine or hydromorphone (US National Institutes of Health clinical trial identifier, NCT01509638).

The study protocol was Institutional Review Board-approved, and the study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation guidelines for good clinical practice. Written informed consent was obtained from all patients before enrollment in the study.

Patients were eligible for inclusion if they were ≥18 years of age and undergoing ileostomy reversal surgery. Key exclusion criteria were pregnancy or unwillingness to use appropriate contraceptive methods; severe hepatic impairment; a history of drug/alcohol abuse; any concomitant condition that, in the opinion of the investigator, could preclude study participation; and intraoperative administration of analgesics (other than fentanyl or analogs), nonsteroidal anti-inflammatory drugs (NSAIDs), local anesthetics (other than liposome bupivacaine), or alvimopan.

Patients were enrolled in sequential cohorts (opioid-based analgesia cohort followed by multimodal analgesia cohort). Screening was conducted within 2 weeks prior to surgery. On the day of surgery (defined as study day 1), PCA was initiated in the opioid analgesia cohort as soon as possible after surgery. Patients in the multimodal analgesia cohort received a single administration of liposome bupivacaine (266 mg in 30 mL of 0.9% normal saline), administered using a moving-needle technique prior to closure, along with ketorolac 30 mg IV (or alternative NSAID equivalent) at the conclusion of surgery, followed by acetaminophen 1000 mg (IV or oral) every 6 hours for 72 hours postsurgery, and oral ibuprofen 600 mg every 6 hours for 72 hours, starting when oral therapy was first tolerated. Liposome bupivacaine was administered evenly between the left and right sides of the surgical wound, with approximately 75% infused into the perifascial region and approximately 25% infused into the junction between the subcutaneous and dermal regions. All patients in both treatment groups had access to rescue analgesia on an as-needed basis, using IV opioid and/or oxycodone/acetaminophen 5 mg/325 mg; acetaminophen use was restricted to ≤4000 mg/day.

PCA and rescue analgesia were continued as needed until hospital discharge. Postsurgical opioid consumption and adverse events (AEs) were recorded through the earlier of 30 days after surgery or hospital discharge. AEs were
recorded through day 30, and follow-up questionnaires were administered on day 30 to evaluate postsurgical complications and patient satisfaction with postsurgical analgesia.

The primary outcome measures included total amount of opioid consumption after surgery, total hospitalization costs, and postsurgical LOS (defined as time in hours from wound closure). These outcomes were assessed until patients were discharged or study day 30, whichever came first. Secondary outcome measures included postsurgical opioid-related AEs (ORAEs), defined as somnolence, respiratory depression, hypoventilation, hypoxia, dry mouth, nausea, vomiting, constipation, sedation, confusion, pruritus, urinary retention, or postoperative ileus; postsurgical AEs (through day 30); patient satisfaction with postsurgical analgesia (assessed on day 30 using a 5-point Likert scale); and patient responses to a four-question survey regarding postsurgical recovery (hospital readmissions, unplanned medical visits, or other health-related problems).

The safety population included all patients who underwent the planned surgery. As per the protocol, all patients who underwent planned surgery and did not receive intraoperative analgesics (other than fentanyl or analogs), local anesthetics, anti-inflammatory agents, or alvimopan were included in the efficacy population. The sample size for the study was not based on formal statistical power calculations. For continuous efficacy measures, between-group comparisons were based on a one-way analysis of variance model after a natural logarithm transformation; two-sided 95% confidence intervals (CIs) were calculated for all differences. All opioid consumption amounts were converted into morphine equivalents before analysis to facilitate comparison. For categorical measures, between-group comparisons were conducted using Fisher’s exact test. Time to event analyses (time to first opioid use and postsurgical LOS) used a log-rank test. All tests for statistical significance were two-sided and were based on a significance level of $P = 0.05$. No adjustments were made for multiple tests.

Results

Forty-three patients underwent surgery as planned and received study treatment as prescribed by the study protocol (efficacy population); 20 were enrolled in the IV opioid PCA group and 23 were enrolled in the liposome bupivacaine-based multimodal analgesia group. Patient demographics and selected baseline characteristics are summarized in Table 1.

Results for the primary efficacy outcome measures are illustrated in Figures 1 to 3. The mean (standard deviation [SD]) amount of postsurgical opioid analgesics consumed was 68 mg (47 mg) in the IV opioid PCA group, compared with 38 mg (46 mg) in the liposome bupivacaine-based multimodal analgesia group ($P = 0.004$; Figure 1). The median (range) LOS after surgery was 3.8 days

| Table 1 Patient demographics and selected baseline characteristics |
|------------------|------------------|------------------|
| Variable         | IV opioid PCA (n = 20) | Liposome bupivacaine-based multimodal analgesia (n = 23) |
| Age, mean (SD), years | 48 (19) | 47 (14) |
| Sex, n (%)       |                   |                   |
| Male             | 13 (65) | 12 (52) |
| Female           | 7 (35) | 11 (48) |
| Race, n (%)      |                   |                   |
| White            | 17 (85) | 23 (100) |
| Black            | 1 (5) | 0 |
| Other            | 2 (10) | 0 |
| Body mass index, mean (SD), kg/m² | 24.2 (3.8) | 23.2 (3.5) |
| ASA physical status classification, n (%) |                   |                   |
| 1                | 0 | 0 |
| 2                | 16 (80) | 15 (65) |
| 3                | 4 (20) | 8 (35) |

Abbreviations: ASA, American Society of Anesthesiologists; IV, intravenous; n, number; PCA, patient-controlled analgesia; SD, standard deviation.

![Figure 1 Postsurgical opioid use.](https://example.com/figure1.png)

**Notes:** Mean total amount (morphine equivalent mg) of postsurgical opioids consumed per patient; error bars represent standard deviation. $P = 0.004$ for the between-group comparison.

**Abbreviations:** IV, intravenous; PCA, patient-controlled analgesia; SD, standard deviation.
in the IV opioid PCA group, compared with 3.0 days (1.4 days–14.6 days) in the multimodal analgesia group ($P = 0.854$; Figure 2). The geometric mean total hospitalization cost was US $6,790 in the IV opioid PCA group compared with US $6,611 in the multimodal analgesia group ($P = 0.8$; Figure 3).

Results for the secondary efficacy outcome measures are summarized in Table 2. The time to first opioid use was significantly longer in the liposome bupivacaine-based multimodal analgesia group compared with the IV opioid PCA group (median: 1.1 hours, versus 0.7 hours; $P = 0.035$). The proportions of patients who were extremely satisfied with postsurgical analgesia and who had postsurgical contact with a health care provider about recovery numerically favored the multimodal analgesia group; the proportion that made unplanned visits with their health care provider was greater in the multimodal analgesia group. However, between-group comparisons showed no statistically significant differences on any of these secondary outcome measures.

Overall, 50% of patients in the IV opioid PCA group experienced ≥1 AE compared with 48% in the liposome bupivacaine-based multimodal analgesia group. The most frequently reported AEs were diarrhea (14% in the IV opioid PCA group versus 12% in the multimodal analgesia group), wound infection (9% versus 4%), and hypokalemia (0% versus 8%). With respect to ORAEs, one patient (5%) in the IV opioid PCA group had an ORAE of vomiting; two patients (8.7%) in the multimodal analgesia group experienced an ORAE (one had constipation; one had urinary retention). No other ORAEs were reported. Three patients in the study, all who were in the multimodal analgesia group, experienced a total of eight serious AEs – all of which were not related to the study drug (one had GI bleeding, one had an anastomotic leak and associated sequelae, and one had a small bowel obstruction and associated sequelae).

Discussion

In this open-label study of patients undergoing ileostomy reversal in an institution with an enhanced recovery patient discharge protocol, the use of liposome bupivacaine-based multimodal analgesia compared with standard opioid-based PCA reduced the mean amount of postsurgical opioid consumption by a statistically significant 43% and extended the time to first opioid use (median: 1.1 hours versus 0.7 hours); the clinical relevance of this small difference in time to first opioid use is unknown. However, we do consider the ∼1-day shorter LOS observed in the multimodal analgesia group to be clinically meaningful, even though the difference versus

![Figure 2 Postsurgical length of stay.](image1)

Notes: Median postsurgical length of hospital stay (days). Error bars represent the range for 95% of values around the median. Postsurgical length of stays ranged from 2.0 days to 6.9 days in the opioid analgesia group and from 1.4 days to 14.6 days in the multimodal analgesia group. $P = 0.854$ for the between-group comparison.

Abbreviations: IV, intravenous; PCA, patient-controlled analgesia.

![Figure 3 Total cost of hospitalization.](image2)

Notes: Geometric least-squares mean per-patient hospitalization costs (US$). $P = 0.8$ for the between-group comparison.

Abbreviations: IV, intravenous; PCA, patient-controlled analgesia.
the opioid-based analgesia group did not reach statistical significance. Mean hospitalization costs were similar between both groups. Because only three ORAEs were reported in this study, no conclusions can be drawn regarding differences in tolerability between the two analgesic regimens that were evaluated. In the multimodal analgesia group, the proportion of patients expressing satisfaction with their postsurgical pain treatment was higher and the proportion who contacted a health care provider regarding postsurgical recovery was lower, but the proportion making unplanned office visits during recovery was lower in the opioid-based analgesia group; none of these differences were statistically significant.

At our institution, patients who undergo ileostomy reversal participate in an enhanced recovery discharge protocol. They do not receive a mechanical bowel preparation preoperatively, and the intraoperative use of bladder catheters and nasogastric tubes is avoided. In the postoperative period, a clear liquid diet is started on the day of surgery and advanced as tolerated. Discharge is allowed when patients are tolerating oral intake and bowel function has commenced with passage of flatus or stool. Except for the enhanced recovery discharge protocol, the design of the current single-center study was identical to the study reported by Marcet et al. The use of liposome bupivacaine-based multimodal analgesia was significant in both the current and Marcet et al study, the percent reduction was less in the current study (relative reduction of 43% in the multimodal group versus the IV opioid PCA group) than in the Marcet et al study, which did not employ an enhanced recovery discharge protocol (relative reduction of 82% for the multimodal analgesia group versus the IV opioid PCA group). As anticipated, the impact of our enhanced recovery discharge protocol was reflected in the reduced median LOS in the opioid PCA group of this study compared with the opioid PCA group in the Marcet et al report (3.8 days versus 5.1 days, respectively). Interestingly, the median LOS for patients receiving liposome bupivacaine-based multimodal analgesia was identical (3.0 days) for both the enhanced recovery and nonenhanced recovery protocol settings.

Important limitations of the current study include its open-label design and the small size of the patient population that was studied, which probably resulted in a lack of statistical power to show between-group differences on most secondary outcome measures. While the use of an open-label design with sequential enrollment (rather than randomized assignment) in the IMPROVE studies could be considered an obvious limitation, this design allowed us to simplify study operations at our institution and to minimize surgeon, patient, and site burden associated with the study. We believe this design made it easier for us to conduct the study in a setting that was as close to “real-world” clinical practice as possible. The use of the fast-track discharge protocol may have also affected the analysis of between-group differences for LOS and hospitalization costs by suppressing variability in maximum values for both measures. The average postsurgical LOS at our institution for this type of surgery is typically about 4 days, consistent with the 3.8-day median LOS observed in the opioid PCA group. That the LOS in the liposome bupivacaine-based multimodal analgesia group was 3.0 days in both this study and the Marcet et al study suggests that we may be reaching the lower limit of how rapidly such patients can be discharged.

**Conclusion**

The use of liposome bupivacaine-based multimodal analgesia in these patients who underwent ileostomy reversal with a fast-track discharge protocol resulted in a significant reduction in mean total amounts of opioids consumed after surgery and a nonsignificant but clinically meaningful reduction in the length of postsurgical hospital stay and total hospitalization costs, compared with a standard opioid-based analgesia regimen.
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Disclosure
The author reports no conflicts of interest in this work.

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