Impact of long-acting local anesthesia on clinical and financial outcomes in laparoscopic colorectal surgery

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Abstract

BACKGROUND: Our objective was to assess clinical and financial outcomes with long-acting liposomal bupicavaine (LB) in laparoscopic colorectal surgery.

METHODS: Patients that received local infiltration with LB were strictly matched to a control group, and compared for postoperative pain, opioid use, length of stay (LOS), hospital costs, and complication, readmission, and reoperation rates.

RESULTS: A total of 70 patients were evaluated in each cohort. Operative times and conversion rates were similar. LB patients had lower post-anesthesia care unit pain scores ($P = .001$) and used less opioids through postoperative day 3 (day 0 $P < .01$; day 1 $P = .03$; day 2 $P = .02$; day 3 $P < .01$). Daily pain scores were comparable. LB had shorter LOS (mean 2.96 vs 3.93 days; $P = .003$) and trended toward lower readmission, complication, and reoperation rates. Total costs/patient were $746 less with LB, a savings of $52,200 across the cohort.

CONCLUSIONS: Using local wound infiltration with LB, opioid use, LOS, and costs were improved after laparoscopic colorectal surgery. The additional medication cost was overshadowed by the overall cost benefits. Incorporating LB into a multimodal pain regiment had a benefit on patient outcomes and health care utilization.

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Pain control is paramount to optimizing postoperative patient care. Inadequate pain control is associated with poor postoperative outcomes, higher risks of readmission, increased health care costs, and lower patient satisfaction.[1]

Pain management is a tenet of enhanced recovery after surgery protocols.[2–9] Recent experience and controlled trials have proven enhanced recovery pathways (ERPs) are the ideal tool to optimize patient and financial outcomes after laparoscopic colorectal surgery.[8,10,11] However, little progress has been made to advance pain management during the time of enhanced recovery with multimodal pain control.

New modalities to manage postoperative pain after laparoscopic surgery include wound infiltration and transversus abdominis plane blocks with local anesthesia.[12–20] Most trials found TAP blocks are effective for reducing immediate postoperative pain and opioid use with an established ERP. However, there these modalities have not optimized pain management. TAP blocks with local anesthesia have not translated to consistently improved outcomes for overall opioid use, pain scores, length of stay (LOS), or readmission rates,[17,18,20–22] and outcomes for local wound infiltration are not well described in the existing literature. One tool to reduce postoperative pain and the need for opioids is wound infiltration with long-acting liposomal bupivacaine (LB).

LB is an extended-release injectable anesthetic approved by the US Food and Drug Administration for single-dose injection into the surgical site to produce postsurgical analgesia for up to 96 hours. The administration and safety of long-acting LB has been previously demonstrated,[23] and efficacy has been described in orthopedics, hemorrhoidectomy, and certain abdominal procedures.[24–34] Furthermore, no prior study evaluated the impact of local wound infiltration with long-acting liposome bupivacaine in regards to patient and financial costs or benefits.

The goal of this study was to evaluate postoperative pain, opioid use, and quality outcomes after laparoscopic colorectal surgery using local wound infiltration with long-acting liposome bupivacaine. Our hypothesis was that local wound infiltration with long-acting liposome bupivacaine as the anesthetic agent results in improved patient and financial outcomes in laparoscopic colorectal surgery with a multimodal ERP.

Methods

After institutional review board approval, review of a prospectively maintained departmental database was performed to identify elective laparoscopic colectomy patients from 2011 to 2014. To reduce variability, a single surgeon performed all cases surgeon through a single-port laparoscopic approach. Patients that received local wound infiltration with LB were matched to a historic control group that received no local wound infiltration on age, gender, body mass index (BMI), diagnosis, procedure performed, surgeon, and operative approach. The control group had no local anesthesia for wound infiltration, as the surgeon's clinical experiences found no benefit with regular bupivacaine, and this was omitted from practice and the ERP before the study period. Patients were excluded if less

than 18 years of age, cases were performed emergently, cases were converted to open intraoperatively, cases were performed through an endoscopic or anorectal approach, or medical records were incomplete. In the experimental group, local wound infiltration with LB was performed at the laparoscopic port site at the end of the procedure. The 20 mL vial of LB (266 mg) was expanded with 20 mL of normal saline and 20 mL of .25% regular bupivacaine to a total volume of 60 mL. The mixture was injected using deep infiltration to the 3 distinct layers of the dermis, deep tissue, and preperitoneal space. Postoperatively, all patients were placed on identical standardized ERPs. This included alvimopan from the preoperative period through the hospital stay, limited intraoperative opioids, glucocorticosteroids, and antiemetics intraoperatively, scheduled nonopioids postoperatively, early oral analgesia and diet, early ambulation, and defined discharge criteria. The full details are summarized in Table 1.

Preoperative patient demographics, perioperative details, and postoperative outcome data were evaluated. Analysis included the 3 postoperative days, as after postoperative day 3, only 5 LB patients remained. Data fields assessed included age, gender, BMI, American Society of Anesthesiologists (ASA) score, indication for operation, operative approach, procedure performed, intraoperative complications, operative time, post-anesthesia care unit (PACU) opiate use, PACU pain scores, daily pain scores, hospital LOS, hospital costs, and readmission, complication, reoperation, and mortality rates within 30 days. The main outcome measures were postoperative pain scores, opioid use, LOS, cost of care, and complication, readmission, and reoperation rates. Cost was defined as the actual total costs for the entire inpatient episode, as reported by our institution's accounting system. Drug utilization was described using the World Health Organization's defined daily dose (DDD) for opioids, with each medication converted to a DDD scale and summed for 1 DDD score per day.[35] The conversion formula for each drug consumed was Fentanyl intravenous (IV) (1 DDD = 100 mcg), Dilaudid IV (1 DDD = 2 mg), Dilaudid per oral (PO) (1 DDD = 4 mg), Oxycodone PO (1 DDD = 20 mg), and Hydrocodone (1 DDD = 10 mg). Pain scores were measures using a visual analog scale (0 to 10), which has been previously described and validated for postoperative pain.[36]

An a priori power analysis was performed to determine the sample size needed to ensure differences between groups were due to LB and not chance alone. With an alpha level of .05, a minimum sample size of 54 was needed to detect differences between the matched groups with 95% power. For statistical analysis, normally distributed data were presented as means (standard deviation), non-normally distributed data as medians (range), and categorical data as frequencies (percent). Univariate analysis was performed using Student's t-test for continuous variables and Fisher's exact test for categorical variables. Statistical significance was defined at a level of alpha less than .05.

Table 1   Enhanced recovery pathway

Preoperative
- Patient counseling and education.
- Selective bowel preparation.
- Gabapentin 300 mg the night before surgery.
- Gabapentin 300 mg PO 2 hr before surgery.
- Celecoxib 400 mg PO 2 hr before surgery.
- Alvimopan 12 mg PO 2 hr before surgery (then 12 mg PO bid until discharge).

Intraoperative
- Dexamethasone 8 mg and acetaminophen 1g IV at induction.
- Toradol 30 mg IV 30 min before emergence.
- Acetaminophen 1g IV 30 min before emergence.
- Zofran 4 mg IV 30 min before emergence.

Postoperative
- Acetaminophen 1 g scheduled q6h (IV until tolerating PO and then transition to 650 mg PO q6h).
- Toradol scheduled 30 mg IV q6h for 48h and then Celecoxib scheduled 400 mg PO bid.
- Gabapentin scheduled 300 mg PO q8 hours.
- Alvimopan scheduled 12 mg PO bid until discharge or a maximum of 7 days.
- Oxycodone 5–10 mg PO q6h as needed for breakthrough pain 4–8/10.
- Dilaudid .4–.6 mg IV q2h as needed for breakthrough pain 8–10/10.
- Clear liquids given as tolerated after surgery until flatus, then advance to a soft, low residue diet.
- Lovenox 40mq SQ daily and PAS stockings.
- Zofran 4 mg IV q6h as needed for nausea.
- Ambulate 3–5 times daily in the hallways.
- Remove Foley on postoperative day 1 in all patients except low pelvic dissections and then remove on postoperative day 2.
- Heplock IV fluids when tolerating adequate PO.

Results

Seventy patients were evaluated in each cohort. Table 2 demonstrates the patient demographic data. The 2 groups were well matched in all demographics. The LB and control groups were comparable in age ($P = .35$), gender ($P = .90$), mean BMI ($P = .60$), and median ASA class ($P = .86$). The main diagnosis in both groups was colon cancer (52.9% LB, 54.4% control; $P = 1.00$), and the most common procedure performed was a segmental colectomy (88.7% LB, 85.8% control; $P = 1.00$).

Perioperative outcomes are summarized in Table 3. The mean operative time (148.0 minutes LB vs 159.3 minutes control; $P = .24$) and mean final incision lengths (3.68 cm LB vs 3.92 control; $P = .67$) were comparable in the experimental and control cohorts. The conversion rate was identical across groups, one case in each cohort was converted to multiport laparoscopy for extensive adhesions. Postoperatively, LB patients had significantly lower mean pain scores in the PACU (1.92 LB vs 4.71 control; $P = .001$). The LB group also used significantly less opioids than the control in the PACU (DDD 1.16 LB vs 3.56 control; $P < .01$) and from postoperative day (POD) 1 through POD 3 (POD 1 $P = .03$; POD 2 $P = .02$; POD 3 $P < .01$). The daily pain scores were comparable across groups (POD 1: 2 LB vs 2.55, control $P = .09$; POD 2: 1.84 LB vs 2.30 control, $P = .20$; POD 3: 1.47 LB vs

2.08 control; $P = .16$). LB patients had a significantly shorter LOS than the control group (mean 2.96 vs 3.93 days; $P = .003$). Postoperatively, LB patients trended toward lower readmission (1.4% LB vs 4.3% control; $P =$

Table 2   Patient demographic data

Variable	LB	Control	P value
N	70	70	—
Mean age (y, SD)	58.7 (13.2)	56.3 (11.7)	.35
Gender (%)	50% M, 50% F	51.4% M, 48.6% F	.90
Mean BMI (kg/m², SD)	26.9 (4.3)	27.3 (4.8)	.60
Median ASA (range)	2 (1–3)	2 (1–3)	.86
Diagnosis (n, %)			1.00
Colon cancer	37 (52.9%)	38 (54.4%)	
Rectal cancer	4 (5.7%)	4 (5.7%)	
Diverticulitis	25 (35.8%)	24 (34.3%)	
Inflammatory bowel disease	2 (2.8%)	2 (2.8%)	
Colonic inertia	2 (2.8%)	2 (2.8%)	
Procedure (n, %)			1.00
Segmental colectomy	62 (88.7%)	60 (85.8%)	
Low anterior resection	4 (6.7%)	6 (8.6%)	
Total abdominal colectomy	2 (2.8%)	2 (2.8%)	
Stoma takedown	2 (2.8%)	2 (2.8%)	

LB = liposomal bupicavaine.

Table 3 Patient perioperative and outcome data

Variable	LB (n = 70)	Control (n = 70)	P value
Mean operative time (min, SD)	148.0 (51.2)	159.3 (51.2)	.24
Mean final incision length	3.68 (1.53)	3.92 (1.39)	.67
Mean PACU pain score (SD)	1.92 (1.82)	4.71 (1.86)	.001
Pain medication use (defined daily dose)			
POD 0	1.16 (.77)	3.56 (14.4)	<.001
POD 1	1.31 (.21)	2.86 (.26)	.031
POD 2	1.28 (.16)	4.91 (3.06)	.02
POD 3	.86 (.17)	2.06 (1.27)	< .001
Daily pain scores			
POD 1	2 (1.67)	2.55 (1.65)	.085
POD 2	1.84 (1.42)	2.30 (1.92)	.20
POD 3	1.47 (1.97)	2.08 (1.67)	.16
Mean direct costs (SD)	$6,851.22 ($3,786.06)	$8,015.04 ($4,241.63)	.24
Mean indirect costs (SD)	$7,298.68 ($3,194.81)	$9,449.27 ($4,356.39)	.02
Mean total costs (SD)	$11,555.66 ($6,740.82)	$12,302.08 ($10,763.59)	.72
Mean length of stay (days, SD)	2.96 (1.25)	3.93 (2.40)	.003
Readmission rate (n, %)	1 (1.4%)	3 (4.3%)	.62
Complication rate (n, %)	2 (2.8%)	6 (7.8%)	.28
Reoperation rate (n, %)	-	2 (2.8%)	.48

LB = liposomal bupicavaine.

.62), complication (2.8% LB vs 7.8% control; $P = .26$), and reoperation rates (0% LB vs 2.8% control; $P = .48$) than controls. The overall mean total costs were $746 lower per patient with LB compared with controls ($11,555.66 LB vs $12,302.08 control; $P = .72$), with significantly lower (mean $2,150) indirect costs ($7,299 LB vs $9,449 control; $P = .02$; Table 3).

Comments

Postoperative pain continues to be an issue impacting postoperative recovery, LOS, and patient satisfaction after laparoscopic colorectal surgery. The increased opioids used to manage postoperative can lead to postoperative ileus and subsequent increases in LOS, health care utilization, and health care costs.[37,38] Multimodal ERPs, where more than one analgesic agents with different mechanisms of action is used to work in synergy, created a paradigm shift to minimize opioid analgesia postoperatively and the concomitant opioid-related adverse events.[27] Long-acting LB is a tool to reduce postoperative pain and opioid utilization by extending the efficacy of local anesthesia. The value of LB has been shown in other procedures, with reductions in opioid use and LOS. However, use of LB continues to be fraught with resistance from the additional $285 expense of the medication. In addition, no prior study evaluated the impact of long-acting liposome bupivacaine in elective laparoscopic colorectal cases. Our goal was to evaluate postoperative pain, opioid use, and quality outcomes after laparoscopic colorectal surgery using local infiltration with long-acting liposome bupivacaine as part of a multimodal ERP. We found patients that received local wound infiltration with long-acting liposome bupivacaine had lower immediate postoperative pain scores and consumed less opioids throughout the hospital stay. Even with less opioid use, pain score for the LB group throughout the hospital stay were low and comparable with the control group. The LB group subsequently had a shorter LOS and lower total hospital costs than the control group. The addition of long-acting LB, an opioid sparing pain management intervention, may be associated with these clinical and financial outcomes.

Use of local anesthesia has been promoted to help reduce postoperative pain, opioids use, and the related adverse effects.[22] Most prior study on the effect of local infiltration for postoperative pain control has been performed in laparoscopic cholecystectomies, a very different procedure than laparoscopic colorectal surgery, and had mixed outcomes.[39–41] Based on clinical experience in colorectal cases, there was no benefit of local wound infiltration with regular bupivacaine, likely due to the short duration of action, and this was omitted from practice and our ERP before the study period. One published study evaluated the impact of local anesthesia after laparoscopic colectomy and supported our findings. Stuhldreher et al[22] compared pain scores, time in the PACU, and PACU opioids consumption in 3 matched elective laparoscopic colorectal surgery cohorts: no local anesthetic; subcutaneous anesthetic at all port and/or wound sites during wound closure (.5% bupivacaine); and subcutaneous anesthetic at all port and/or wound sites with intraperitoneal infiltration (1% lidocaine). The authors found use of local anesthetic, either subcutaneous or subcutaneous combined with intraperitoneal, did not significantly decrease postoperative pain scores, opioid requirements, time in the PACU, or hospital

LOS across the three study groups.[22] No prior studies with laparoscopic colorectal resections have been performed using LB as the anesthetic agent.

In the few published studies using LB as the anesthetic agent, it demonstrated promising benefits in postoperative pain control, decreasing LOS, opioid-related complications, and increasing patient satisfaction.[42] Haas et al[31] showed the efficacy of LB in significantly reducing postoperative pain scores, opioid consumption, and increasing the interval to first opioid use compared with bupivacaine HCl. Vogel[34] found LB significantly lowered opioid use in ileostomy reversal patients after an ERP; however, there were no significant decreases in LOS or total hospital costs compared with the group that received IV opioid-based patient-controlled analgesia with no LB. Marcet et al[32] also found significantly shorter LOS and opioid consumption in LB vs a standard IV opioid-based regimen in ileostomy reversal patients, but the authors also had significantly lower hospital costs in the LB group. In open colectomy patients, Cohen[27] discovered significantly less opioid utilization, lower average total cost, and shorter median LOS with LB. Although these results show the promise of LB, our study is the first to use of LB in laparoscopic colorectal resections where all patient follow a standardized ERP, making it applicable and generalization to current practices. Furthermore, no prior study has demonstrated that LB improves patient recovery and reduces hospital LOS in laparoscopic colorectal surgery.

In our study, the LB group had reduced pain scores in the PACU (mean 1.92 vs 4.71; $P = .001$). The LB group used significantly less opioids through POD 3 (POD 0: $P < .01$; POD 1: $P = .031$; POD 2 $P = .016$; POD 3 $P < .01$). Even with less opioid consumption, pain scores were lower or comparable (POD 1: 2 vs 2.55, $P = .08$; POD 2: 1.84 vs 2.30, $P = .20$; POD 3: 1.47 vs 2.08; $P = .16$). The LB group also had a significantly shorter LOS (mean 2.96 vs 3.93 days; $P = .003$). The reduced opioid consumption may translate to faster recovery, as opioids and opioid-induced bowel dysfunction delays recovery of normal colonic motility, prolongs postoperative ileus, and increases morbidity.[43] Both the experimental and control groups used a single incision laparoscopic technique, and the groups were matched on the procedure performed, controlling for bias. With this technique and the opioid-sparing multimodal ERP, the pain medication used, pain scores, and LOS in the control group were commendably low at baseline, thus the ability to show improvement with the intervention in the experimental group is even more meaningful. At last, there were lower means total costs of $746 less per patient with LB. The major opposition to LB is the additional medication cost. The patient cost of a vial of LB (266 mg/20 mL) is $285. Although this is an additional pharmacy expense, our results demonstrate an overall cost savings and greater benefit for patients using LB than the control group without LB with a standardized recovery pathway in laparoscopic colorectal surgery.

We recognize the limitations in this study. The study design matched patients on demographic and operative variables to ensure the groups were comparable, but the study was not a randomized controlled trial. Thus, it is still susceptible to the biases of a case matched study. Although the specific elements and timing of administration of each element in the ERP were similar in the matched groups, compliance with the ERP over time may have been a factor impacting the outcomes, as the control group was from an earlier period when the ERP was less mature. With this study design, it was also not possible to directly relate the outcomes to the use of LB. The promising results seen in the LB group should draw support for future controlled studies. After postoperative day 3, only 5 LB patients remained; therefore, we only compared the LB and control groups through the first 3 postoperative days. To control for variability, the study follows a single surgeon, which may impact the generalizability of the study. In addition, control group preceded the LB group, and whereas the same ERP was used in both groups, it is possible there were differences with compliance over time that could impact outcomes. The difference in total costs was also not statistically significant. However, even with the additional medication cost of LB included, the mean total cost savings for the 70-patient LB cohort was $52,249.40. The point should also be made that the visual analogue scale scores and LOS were low in both cohorts, which may be attributed to the use of a (single incision) laparoscopic approach with an ERP. This may be a limitation to finding significant differences between groups but is truly a benefit for all patients included.

In conclusion, local wound infiltration with LB made an impact on patient, financial, and quality outcomes. The LB group consumed significantly less opioids throughout the hospital stay with comparable pain scores. LB patients subsequently had a faster recovery, with a shorter LOS than the control group, and trends toward lower readmission, complication, and reoperation rates. The $285 additional medical cost of LB was overshadowed by the $746 overall cost savings per patient compared with the control group, a savings of $52,249 across the entire cohort. LB appears to have a benefit on patient outcomes and health care utilization. Future controlled studies are needed for definitive recommendations on the use of LB.

References

1. Joshi GP, Beck DE, Emerson RH, et al. Defining new directions for more effective management of surgical pain in the United States: highlights of the inaugural Surgical Pain Congress. Am Surg 2014;80:219–28.
2. Delaney CP, Zutshi M, Senagore AJ, et al. Prospective, randomized, controlled trial between a pathway of controlled rehabilitation with early ambulation and diet and traditional postoperative care after laparotomy and intestinal resection. Dis Colon Rectum 2003;46:851–9.
3. Delaney CP, Brady K, Woconish D, et al. Towards optimizing perioperative colorectal care: outcomes for 1,000 consecutive laparoscopic

colon procedures using enhanced recovery pathways. Am J Surg 2012; 203:353–5; discussion 355–6.

4. Fierens J, Wolthuis AM, Penninckx F, et al. Enhanced recovery after surgery (ERAS) protocol: prospective study of outcome in colorectal surgery. Acta Chir Belg 2012;112:355–8.

5. Gustafsson UO, Scott MJ, Schwenk W, et al. Guidelines for perioperative care in elective colonic surgery: Enhanced Recovery After Surgery (ERAS(R)) Society recommendations. Clin Nutr 2012;31: 783–800.

6. Kehlet H, Wilmore DW. Evidence-based surgical care and the evolution of fast-track surgery. Ann Surg 2008;248:189–98.

7. Lassen K, Soop M, Nygren J, et al. Consensus review of optimal perioperative care in colorectal surgery: Enhanced Recovery After Surgery (ERAS) Group recommendations. Arch Surg 2009;144:961–9.

8. Vlug MS, Wind J, Hollmann MW, et al. Laparoscopy in combination with fast track multimodal management is the best perioperative strategy in patients undergoing colonic surgery: a randomized clinical trial (LAFA-study). Ann Surg 2011;254:868–75.

9. Wind J, Polle SW, Fung Kon Jin PH, et al. Systematic review of enhanced recovery programmes in colonic surgery. Br J Surg 2006; 93:800–9.

10. Adamina M, Kehlet H, Tomlinson GA, et al. Enhanced recovery pathways optimize health outcomes and resource utilization: a meta-analysis of randomized controlled trials in colorectal surgery. Surgery 2011;149:830–40.

11. Adamina M, Senagore AJ, Delaney CP, et al. A systematic review of economic evaluations of enhanced recovery pathways for colorectal surgery. Ann Surg; 2014.

12. Joshi GP, Bonnet F, Kehlet H. Evidence-based postoperative pain management after laparoscopic colorectal surgery. Colorectal Dis 2013;15: 146–55.

13. Petersen PL, Mathiesen O, Torup H, et al. The transversus abdominis plane block: a valuable option for postoperative analgesia? A topical review. Acta Anaesthesiol Scand 2010;54:529–35.

14. Abdallah FW, Chan VW, Brull R. Transversus abdominis plane block: a systematic review. Reg Anesth Pain Med 2012;37:193–209.

15. Conaghan P, Maxwell-Armstrong C, Bedforth N, et al. Efficacy of transversus abdominis plane blocks in laparoscopic colorectal resections. Surg Endosc 2010;24:2480–4.

16. Favuzza J, Delaney CP. Outcomes of discharge after elective laparoscopic colorectal surgery with transversus abdominis plane blocks and enhanced recovery pathway. J Am Coll Surg 2013;217:503–6.

17. Johns N, O'Neill S, Ventham NT, et al. Clinical effectiveness of transversus abdominis plane (TAP) block in abdominal surgery: a systematic review and meta-analysis. Colorectal Dis 2012;14:e635–42.

18. Keller DS, Ermlich BO, Schiltz N, et al. The effect of transversus abdominis plane blocks on postoperative pain in laparoscopic colorectal surgery: a prospective, randomized, double-blind trial. Dis Colon Rectum 2014;57:1290–7.

19. Siddiqui MR, Sajid MS, Uncles DR, et al. A meta-analysis on the clinical effectiveness of transversus abdominis plane block. J Clin Anesth 2011;23:7–14.

20. Walter CJ, Maxwell-Armstrong C, Pinkney TD, et al. A randomised controlled trial of the efficacy of ultrasound-guided transversus abdominis plane (TAP) block in laparoscopic colorectal surgery. Surg Endosc 2013;27:2366–72.

21. Charlton S, Cyna AM, Middleton P, et al. Perioperative transversus abdominis plane (TAP) blocks for analgesia after abdominal surgery. Cochrane Database Syst Rev; 2010:CD007705.

22. Stuhldreher JM, Adamina M, Konopacka A, et al. Effect of local anesthetics on postoperative pain and opioid consumption in laparoscopic colorectal surgery. Surg Endosc 2012;26:1617–23.

23. Bergese SD, Onel E, Portillo J. Evaluation of DepoFoam((R)) bupivacaine for the treatment of postsurgical pain. Pain Manag 2011;1:539–47.

24. Barrington JW, Dalury DF, Emerson RHJ, et al. Improving patient outcomes through advanced pain management techniques in total hip and knee arthroplasty. Am J Orthop (Belle Mead NJ) 2013;42:S1–20.

25. Berend ME, Berend KR, Lombardi AV. Advances in pain management: game changers in knee arthroplasty. Bone Joint J 2014;96-B:7–9.

26. Candiotti K. Liposomal bupivacaine: an innovative nonopioid local analgesic for the management of postsurgical pain. Pharmacotherapy 2012;32:19S–26S.

27. Cohen SM. Extended pain relief trial utilizing infiltration of Exparel((R)), a long-acting multivesicular liposome formulation of bupivacaine: a Phase IV health economic trial in adult patients undergoing open colectomy. J Pain Res 2012;5:567–72.

28. Domb BG, Gupta A, Hammarstedt JE, et al. The effect of liposomal bupivacaine injection during total hip arthroplasty: a controlled cohort study. BMC Musculoskelet Disord 2014;15:310.

29. Fayezizadeh M, Petro CC, Rosen MJ, et al. Enhanced recovery after surgery pathway for abdominal wall reconstruction: pilot study and preliminary outcomes. Plast Reconstr Surg 2014;134:151S–9S.

30. Gorfine SR, Onel E, Patou G, et al. Bupivacaine extended-release liposome injection for prolonged postsurgical analgesia in patients undergoing hemorrhoidectomy: a multicenter, randomized, double-blind, placebo-controlled trial. Dis Colon Rectum 2011;54:1552–9.

31. Haas E, Onel E, Miller H, et al. A double-blind, randomized, active-controlled study for post-hemorrhoidectomy pain management with liposome bupivacaine, a novel local analgesic formulation. Am Surg 2012;78:574–81.

32. Marcet JE, Nfonsam VN, Larach S. An extended paIn relief trial utilizing the infiltration of a long-acting Multivesicular liPosome foRmulation Of bupiVacaine, EXPAREL (IMPROVE): a phase IV health economic trial in adult patients undergoing ileostomy reversal. J Pain Res 2013;6:549–55.

33. Morales RJ, Mentz Hr, Newall G, et al. Use of abdominal field block injections with liposomal bupivicaine to control postoperative pain after abdominoplasty. Aesthet Surg J 2013;33:1148–53.

34. Vogel JD. Liposome bupivacaine (EXPAREL(R)) 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. J Pain Res 2013;6:605–10.

35. Purpose of the Defined Daily Dose system. World Health Organization. Avaliable at: http://www.whocc.no/atc_ddd_methodology/purpose_of_the_atc_ddd_system/. Accessed October 1, 2015.

36. Sjostrom B, Dahlgren LO, Haljamae H. Strategies in postoperative pain assessment: validation study. Intensive Crit Care Nurs 1999;15: 247–58.

37. Carroll J, Alavi K. Pathogenesis and management of postoperative ileus. Clin Colon Rectal Surg 2009;22:47–50.

38. Senagore AJ. Pathogenesis and clinical and economic consequences of postoperative ileus. Clin Exp Gastroenterol 2010;3:87–9.

39. Louizos AA, Hadzilia SJ, Leandros E, et al. Postoperative pain relief after laparoscopic cholecystectomy: a placebo-controlled double-blind randomized trial of preincisional infiltration and intraperitoneal instillation of levobupivacaine 0.25%. Surg Endosc 2005;19:1503–6.

40. Wills VL, Hunt DR. Pain after laparoscopic cholecystectomy. Br J Surg 2000;87:273–84.

41. Sarac AM, Aktan AO, Baykan N, et al. The effect and timing of local anesthesia in laparoscopic cholecystectomy. Surg Laparosc Endosc 1996;6:362–6.

42. Tong YC, Kaye AD, Urman RD. Liposomal bupivacaine and clinical outcomes. Best Pract Res Clin Anaesthesiol 2014;28:15–27.

43. Ali SZ, Kurz A. Methylnaltrexone and alvimopan: economic management of opioid-induced bowel dysfunction. Expert Rev Pharmacoecon Outcomes Res 2004;4:153–7.