Retrospective analysis of quality improvement when using liposome bupivacaine for postoperative pain control

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Background/objective: Liposome bupivacaine, a prolonged-release bupivacaine formulation, recently became available at the Naval Medical Center San Diego (NMCSD); before availability, postsurgical pain for large thoracic/abdominal procedures was primarily managed with opioids with/without continuous thoracic epidural (CTE) anesthesia. This retrospective chart review was part of a clinical quality initiative to determine whether postsurgical outcomes improved after liposome bupivacaine became available.

Methods: Data from patients who underwent laparotomy, sternotomy, or thoracotomy at NMCSD from May 2013 to May 2014 (after liposome bupivacaine treatment became available) were compared with data from patients who underwent these same procedures from December 2011 to May 2012 (before liposome bupivacaine treatment became available). Collected data included demographics, postoperative pain control methods, opioid consumption, perioperative pain scores, and lengths of intensive care unit and overall hospital stays.

Results: Data from 182 patients were collected: 88 pre-liposome bupivacaine (laparotomy, n=52; sternotomy, n=26; and thoracotomy, n=10) and 94 post-liposome bupivacaine (laparotomy, n=49; sternotomy, n=31; and thoracotomy, n=14) records. Mean hospital stay was 7.0 vs 5.8 days (P=0.009) in the pre- and post-liposome bupivacaine groups, respectively, and mean highest reported postoperative pain score was 7.1 vs 6.2 (P=0.007), respectively. No other significant between-group differences were observed for the overall population. In the laparotomy subgroup, there was a reduction in the proportion of patients who received CTE anesthesia post-liposome bupivacaine (22% [11/49] vs 35% [18/52] pre-liposome bupivacaine).

Conclusion: Surgeons and anesthesiologists have changed the way they manage postoperative pain since the time point that liposome bupivacaine was introduced at NMCSD. Our findings suggest that utilization of liposome bupivacaine may be a useful alternative to epidural anesthesia.

Keywords: laparotomy, thoracotomy, sternotomy, anesthesia, local

Introduction

Postsurgical pain is a significant concern for patients undergoing inpatient and outpatient procedures at US hospitals. In a recent survey regarding pre- and postsurgical pain experiences of patients (N=300) from randomly selected surgical practices across the US, pain after surgery was the most prominent presurgery concern expressed by patients in the sample; 80% reported having concerns about postsurgical pain, and 46% indicated that these concerns resulted in “high” or “very high” levels of anxiety.1 Such concerns are well founded, because approximately two-thirds of respondents reported experiencing postsurgical pain of moderate-to-extreme intensity.1
The inadequacy of postsurgical pain control has been recognized for decades,\(^1\) and numerous government agencies and clinical societies have published recommendations with strategies intended to improve postsurgical analgesia practices.\(^2,3\) The American Pain Society, in collaboration with the Pain Care Coalition,\(^4\) has also advocated for the creation of a national pain and palliative care research and quality program that would ensure that military personnel, veterans, and Medicare beneficiaries receive appropriate pain management.\(^5\) However, despite these efforts, there appears to have been little or no improvement in patients’ reported levels of postsurgical pain control over the past 20 years.\(^6\)

Opioid analgesics are a cornerstone of postsurgical pain management\(^7,8\) because these agents are widely recognized as the most effective option for controlling moderate-to-severe pain.\(^7,8\) However, commonly reported opioid-related adverse events (ORAEs), including constipation, nausea, and vomiting, can be burdensome,\(^7,9\) especially in the setting of abdominal surgery.\(^10,11\) In addition, health care costs have been reported to be higher for patients who experience ORAEs because of increased pharmacy and nursing requirements and increased length of hospital stay.\(^7,9\) To minimize the risk of ORAEs while still providing adequate postsurgical pain control, the American Society of Anesthesiologists (ASA) recommends the use of multimodal approaches to pain management that incorporate perioperative infiltration of local anesthetics into surgical incision sites whenever possible.\(^3\)

Historically, postsurgical analgesia regimens used at the Naval Medical Center San Diego (NMCSD) for patients undergoing chest or abdominal surgery consisted of opioids as the most effective option for controlling moderate-to-severe pain.\(^7,8\) However, commonly reported opioid-related adverse events (ORAEs), including constipation, nausea, and vomiting, can be burdensome,\(^7,9\) especially in the setting of abdominal surgery.\(^10,11\) In addition, health care costs have been reported to be higher for patients who experience ORAEs because of increased pharmacy and nursing requirements and increased length of hospital stay.\(^7,9\) To minimize the risk of ORAEs while still providing adequate postsurgical pain control, the American Society of Anesthesiologists (ASA) recommends the use of multimodal approaches to pain management that incorporate perioperative infiltration of local anesthetics into surgical incision sites whenever possible.\(^3\)

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Methods

Study design

This analysis was based on a retrospective chart review performed for CQI purposes. As such, CQI was implemented as part of practices administered to improve patient care at NMCSD; the analysis was not required to go through a formal institutional review board process or obtain informed consent, as per guidance from the US Department of Health and Human Services.\(^21\) Data from all patients who underwent laparotomy, sternotomy, or thoracotomy procedures during the 12 months after liposome bupivacaine became available at NMCSD (May 2013 through May 2014; post-liposome bupivacaine group) were compared with data from patients who underwent these same surgical procedures during the 6 months before the introduction of liposome bupivacaine at NMCSD (December 2011 through May 2012; pre-liposome bupivacaine group). Patients were identified for inclusion using current procedural terminology (CPT\(^\text{®}\)) codes for laparotomy, sternotomy, and thoracotomy (Table 1). Pain control methods used in these surgical procedures included CTE anesthesia (laparotomy patients only), TAP block, wound infiltration with liposome bupivacaine, and wound infiltration via elastomeric pump (used prior to formulary adoption of liposome bupivacaine for thoracotomy procedures; patients received a continuous infusion of bupivacaine HCl into their surgical wound for 3 days after surgery).

Outcomes

Each medical record was reviewed and relevant data were extracted for each patient. Collected demographic and baseline clinical characteristics included age, sex, ASA physical status classification score, and preoperative pain score on an
eleven-point numeric rating scale (NRS; 0= no pain to 10= worst pain imaginable). Pain scores captured in nursing notes were also recorded at 4-hour intervals during the first 72 hours after surgery. Postsurgical consumption of intravenous and oral opioids (converted to oral morphine equivalents) was recorded for each patient; drugs used included morphine, hydromorphone, fentanyl, meperidine, hydrocodone, and oxycodone. Length of ICU stay and total hospital length of stay (both in days) were recorded for each patient.

Data analysis

Data for patients in the pre- and post-liposome bupivacaine groups were stratified by surgery type (laparotomy, sternotomy, or thoracotomy). Additional subset analyses were performed for the laparotomy group based on pain control method (CTE anesthesia or no CTE in the pre-liposome bupivacaine group, and CTE anesthesia only or liposome bupivacaine only in the post-liposome bupivacaine group). Epidural use was not an option for sternotomy or thoracotomy procedures.

Comparisons between the pre- and post-liposome bupivacaine groups were made for the outcomes of overall mean and highest mean pain scores through 72 hours postsurgery, opioid use (milligrams of oral morphine equivalents), length of ICU stay, and length of hospital stay. Data were summarized using descriptive statistics. The between-group comparisons were conducted using a t-test, with the significance level set at P<0.05.

Results

Patients

A total of 182 patients were included in the analysis: 88 in the pre-liposome bupivacaine group (laparotomy, n=52; sternotomy, n=26; and thoracotomy, n=10) and 94 in the post-liposome bupivacaine group (laparotomy, n=49; sternotomy, n=31; and thoracotomy, n=14). Of the laparotomy patients in the post-liposome bupivacaine group, eleven received a CTE anesthesia and 38 did not. Of the laparotomy patients in the pre-liposome bupivacaine group, 18 received CTE anesthesia and 34 did not.

Table 1 (Continued)

| Code  | Description                                      |
|-------|--------------------------------------------------|
| 32141 | Incision procedures on the lungs and pleura (remove bullae) |

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32666 Thoracotomy (VATS) on the lungs and pleura

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Abbreviation: VATS, video-assisted thoracic surgery.
Patient demographic and baseline clinical characteristics are summarized in Table 2. The groups were relatively well matched at baseline, with the exception of preoperative pain scores, which were significantly lower in the overall post-liposome bupivacaine group, as well as in the laparotomy and sternotomy subgroups. A greater proportion of patients had severe pain (NRS score ≥7) preoperatively during the pre-liposome bupivacaine period (10% [9/88]) compared with patients who underwent surgery during the post-liposome bupivacaine period (2% [2/94]).

### Results for overall groups
Mean (standard deviation [SD]) pain scores during the first 72 hours after surgery were similar in the pre-liposome bupivacaine group (2.3 [1.2]) compared with the post-liposome bupivacaine group (2.3 [1.8]; \( P=0.33 \)). However, the mean (SD) highest pain score was significantly higher in the pre-liposome bupivacaine group (7.1 [2.3]) than in the post-liposome bupivacaine group (6.2 [2.6]; \( P=0.007 \)).

Mean (SD) amounts of opioids (oral morphine equivalents) consumed were similar in the pre- and post-liposome bupivacaine groups (291 [309] vs 263 [227] mg; \( P=0.64 \)). Mean (SD) duration of ICU stay was also similar in the two treatment groups (1.9 [2.1] vs 1.8 [2.1] days; \( P=0.61 \)), but mean (SD) duration of hospital stay was more than a full day longer in the pre-liposome bupivacaine group (7.0 [3.4] days) than in the post-liposome bupivacaine group (5.8 [2.7] days; \( P=0.009 \)).

### Results for subgroups stratified by type of surgery
Mean pain scores, postsurgical opioid use, and lengths of ICU and hospital stay results are summarized in Table 3. In patients who underwent laparotomy, mean length of hospital stay was significantly shorter in the post-liposome bupivacaine group (5.8 days) compared with the pre-liposome bupivacaine group (7.4 days; \( P=0.027 \)). In patients who underwent sternotomy, the mean maximum postsurgical pain intensity score was significantly lower in the post-liposome bupivacaine group (5.7) compared with the pre-liposome bupivacaine group (7.2; \( P=0.039 \)). No other statistically significant between-group differences were observed. However, there was a trend toward reduced postsurgical opioid use in the post-liposome bupivacaine group in the subset of patients who underwent laparotomy, mean length of hospital stay was significantly shorter in the pre-liposome bupivacaine group (7.1 [2.3]) than in the post-liposome bupivacaine group (7.4 days; \( P=0.027 \)).

### Results for subset analyses of laparotomy patients
Results for mean pain scores, postsurgical opioid use, and lengths of ICU and hospital stays for laparotomy patients stratified by pain control method are summarized in Table 4. On average, length of hospital stay was significantly shorter (by ∼1 day; \( P=0.028 \)) in patients who received CTE anesthesia during the period when liposome bupivacaine was available compared with the time period before liposome bupivacaine became available.

An analysis of data from the pre-liposome bupivacaine period showed that patients who received CTE anesthesia...
Table 3 Results for subgroups stratified by type of surgery

| Parameter                                      | Laparotomy                                  | Sternotomy                                  | Thoracotomy                                 |
|------------------------------------------------|---------------------------------------------|---------------------------------------------|---------------------------------------------|
|                                                | Pre-liposome bupivacaine (n=52)              | Post-liposome bupivacaine (n=49)             | Pre-liposome bupivacaine (n=10$^a$)          | Post-liposome bupivacaine (n=14)             |
| Mean pain intensity score                      | 2.2                                         | 2.4                                         | 2.5                                         | 2.3                                         |
| Mean maximum pain intensity score              | 7.0                                         | 6.4                                         | 7.2                                         | 6.7                                         |
| Mean total amount of orally administered postsurgical opioids (milligram morphine equivalents) | 345                                         | 232                                         | 192                                         | 268                                         |
| Number of patients admitted to ICU, n (%)      | 18 (35)                                     | 19 (39)                                     | 26 (100)                                    | 30 (97)                                     |
| Mean length of ICU stay (days)                 | 1.0                                         | 0.8                                         | 3.8                                         | 3.3                                         |
| Mean length of hospital stay (days)            | 7.4                                         | 5.8$^b$                                     | 6.6                                         | 6.0                                         |

Notes: $^a$Patients received continuous infusion of local anesthetic via elastomeric pump. $^b$P<0.05 vs pre-liposome bupivacaine group. Abbreviation: ICU, intensive care unit.

had significantly longer mean ICU stays and longer mean hospital stays than patients who did not receive CTE anesthesia ($P<0.05$ for both comparisons; Table 4). However, those who received CTE anesthesia reported lower mean pain intensity scores ($P=0.037$).

Among patients who underwent laparotomy during the period when liposome bupivacaine was available, those who received liposome bupivacaine had a significantly shorter mean duration of ICU and hospital stay than those who received CTE anesthesia ($P<0.05$ for both comparisons; Table 4). No statistically significant between-group differences were observed in mean pain scores or amount of mean postsurgical oral opioids consumed in these two patient subsets.

Discussion

Local anesthetic wound infiltration and TAP block are gaining acceptance as simple and effective techniques to manage postoperative pain following a variety of open and laparoscopic procedures.$^{22-24}$ Wound infiltration analgesia is typically administered as a single injection at the end of an operation while patients are under general or regional anesthesia,$^{22}$ while TAP block is injected into the neurovascular plane of the abdominal musculature.$^{25}$ Multimodal analgesia regimens that include wound infiltration or TAP blocks with local anesthetics are reported to be associated with decreased postoperative pain scores, reduced opioid consumption, fewer ORAEs, earlier patient mobility, shorter hospital stays, and greater patient satisfaction compared with other pain management strategies.$^{22,23,26-28}$ Side effects and surgical complications are infrequent, and systemic toxicity is rare with TAP block or wound infiltration of local anesthetics; in contrast, epidural approaches can be associated with unwanted motor blockade, bladder dysfunction, and other potentially serious complications.$^{24,26,27,29-33}$ In addition, local infiltration and TAP block techniques are easier to administer.

Table 4 Results for subset analyses of patients who underwent laparotomy

| Parameter                                      | Pre-liposome bupivacaine, CTE (n=18) | Pre-liposome bupivacaine, No CTE (n=34) | Post-liposome bupivacaine, CTE only (n=11) | Post-liposome bupivacaine, liposome bupivacaine only (n=38) |
|------------------------------------------------|--------------------------------------|-----------------------------------------|---------------------------------------------|------------------------------------------------------------|
| Mean pain intensity score                       | 1.6                                  | 2.6$^c$                                 | 2.4                                         | 2.5                                         |
| Mean maximum pain intensity score               | 6.2                                  | 7.4$^c$                                 | 7.1                                         | 6.2                                         |
| Mean total amount of orally administered postsurgical opioids (milligram morphine equivalents) | 242                                  | 400                                     | 226                                         | 234                                         |
| Mean length of ICU stay (days)                  | 1.7                                  | 0.7$^c$                                 | 1.5                                         | 0.6$^c$                                     |
| Mean length of hospital stay (days)             | 8.9                                  | 6.6$^c$                                 | 7.7$^c$                                     | 5.3$^c$                                     |

Notes: $^a$P=0.037 vs laparotomy pre-liposome bupivacaine CTE group. $^b$P=0.04 vs laparotomy pre-liposome bupivacaine CTE group. $^c$P=0.02 vs laparotomy post-liposome bupivacaine CTE only group. $^d$P=0.03 vs laparotomy pre-liposome bupivacaine CTE group. $^e$P=0.028 vs laparotomy pre-liposome bupivacaine CTE group. $^f$P=0.03 vs laparotomy post-liposome bupivacaine CTE only group. Abbreviations: CTE, continuous thoracic epidural; ICU, intensive care unit.
than epidural analgesia and do not require special expertise to perform.\textsuperscript{23,30} TAP blocks can also be used for patients undergoing major surgery who have contraindications to epidural analgesia (eg, those with clotting disorders or sepsis).\textsuperscript{27,28} Based on these findings from the medical literature, we postulated that incorporating liposome bupivacaine into multimodal analgesia regimens for postsurgical pain management at NMCSD could result in CQI at our facility. This retrospective chart review was undertaken to compare postsurgical outcomes before and after liposome bupivacaine became available at NMCSD.

Findings from our analysis suggest that overall, the quality of postsurgical analgesia (mean pain intensity scores and amounts of orally administered opioids consumed) was similar during the pre- and post-liposome bupivacaine periods, but the average length of hospital stay was significantly shorter during the post-liposome bupivacaine period. This difference was apparently driven by the between-group difference in the laparotomy surgery subgroups, which represent the largest patient populations in the study. The number of patients included in the sternotomy and thoracotomy surgery treatment groups may have been too small to show statistically significant differences on this parameter.

Interestingly, the use of CTE anesthesia decreased after liposome bupivacaine became available at NMCSD. During the pre-liposome bupivacaine period, 35\% (18/52) of patients received CTE anesthesia compared with 22\% (11/49) of patients during the post-liposome bupivacaine period. This is noteworthy because of the potential safety concerns associated with the use of CTE anesthesia (eg, spinal hematoma, abscess, and permanent neurologic damage).\textsuperscript{33} Avoiding the use of CTE anesthesia can be particularly useful in cases wherein anticoagulation, ambulation requirements, hemodynamic concerns, or inpatient epidural management requirements may preclude the use of epidurals.\textsuperscript{33–35} Some anesthesiologists have indicated that they are performing fewer epidural procedures, in large part due to fear of litigation and lack of evidence supporting clinical benefits compared with other less-invasive pain management strategies.\textsuperscript{35} Analgesic techniques that allow for avoidance of continuous infusion modalities and/or are associated with shorter hospital stays may lead to decreased health care costs. While formal cost analyses were not conducted in this study, even a 1-day reduction in hospital stay would be expected to result in significant cost savings. Based on data from a recent survey of clinicians and economic professionals from US hospitals, the average hospital cost per day following inpatient general/colorectal surgery is \$2,000.\textsuperscript{36} Findings from the same survey\textsuperscript{56} indicate that the estimated average direct cost per hospital stay for a patient who uses intravenous opioid patient-controlled analgesia is \$600, plus an average of \textasciitilde4 hours of staff time associated with administration, documentation, and monitoring. The direct cost associated with continuous infusion of local anesthetics via elastomeric pumps is \$650 per patient plus \textasciitilde3 hours of staff time associated with administration, documentation, and monitoring, while the direct cost of a 266 mg/20 mL vial of liposome bupivacaine is \$300. Assuming that a similar level of analgesia is achieved with each modality, use of liposome bupivacaine could lead to meaningful cost savings (~\$300 per patient or \$300,000 per 1,000 patients). Furthermore, findings from a series of open-label economic studies support the use of liposome bupivacaine-based multimodal analgesic regimens over intravenous opioid-based regimens for postsurgical analgesia in patients undergoing open colectomy,\textsuperscript{17} laparoscopic colectomy,\textsuperscript{18} and ileostomy reversal.\textsuperscript{39,40} A pooled analysis of data from the 191 patients (liposome bupivacaine-based multimodal analgesia, n=86; intravenous opioid-based analgesia, n=105) across these studies showed that the multimodal analgesia group had significantly less mean postsurgical opioid consumption (38 vs 96 mg morphine equivalents; \textit{P}<0.0001), shorter median hospital length of stay (2.9 vs 4.3 days; \textit{P}<0.0001), and lower mean hospitalization costs ($8,271 vs $10,726; \textit{P}=0.011), compared with intravenous opioid-based analgesia.\textsuperscript{16}

There are several limitations to the interpretation of results from our analysis. The study was inherently limited by its retrospective observational design, which could not control for possible selection bias (eg, sicker/more complex patients may have been more likely to receive CTE anesthesia than healthier patients). Moreover, the results were derived from patients who were treated at a single institution; our observations may not be generalizable to other institutions or patient populations. Finally, there are several potential factors other than the intervention studied that could have contributed to the observed results (eg, other improvements in surgical or postoperative practices may have occurred between December 2011 and May 2014, which could have influenced the results). It should also be noted that although the characteristics of the patient groups treated during the pre- and post-liposome bupivacaine periods of the study were generally similar, mean preoperative pain intensity scores were significantly higher in the pre-liposome bupivacaine group (2.0) compared with the post-liposome bupivacaine group (0.7; \textit{P}=0.001). This difference was primarily driven by a higher number of outliers in the post-liposome bupivacaine group. Larger, prospective,
controlled studies are needed to confirm the reproducibility of these findings across a heterogeneous range of patient populations and surgical practices.

Conclusion
This analysis allowed us to observe how our surgeons and anesthesiologists have changed the way they manage postoperative pain after liposome bupivacaine was introduced at NMCSD. Since the time point that liposome bupivacaine became available, there has been a noticeable decrease in the use of CTE anesthesia. Given the relative simplicity of administration and the seemingly comparable efficacy for postsurgical analgesia, liposome bupivacaine may be a useful alternative to epidural anesthesia.

Acknowledgments
Editorial assistance was provided by Michael D Morren, RPh of Peloton Advantage, LLC, Parsippany, NJ, USA, supported by Pacira Pharmaceuticals, Inc, the manufacturer of liposome bupivacaine (bupivacaine liposome injectable suspension; EXPAREL®). The authors are fully responsible for the content, editorial decisions, and opinions expressed in this article. The authors did not receive any honorarium related to the development of this manuscript.

The results of this study were presented at the meetings of the American Academy of Pain Medicine held in National Harbor, MD, USA, from March 19 to March 22, 2015; the American Society of Regional Anesthesia and Pain Medicine held at Caesars Palace, Las Vegas, NV, USA, from May 14 to May 16, 2015; and the Academic Research Competition held in May 2015 in San Diego, CA, USA.

Disclosure
The authors report no conflicts of interest in this work.

References
1. Gan TJ, Habib AS, Miller TE, White W, Apfelbaum JL. Incidence, patient satisfaction, and perceptions of post-surgical pain: results from a US national survey. *Curr Med Res Opin*. 2014;30(1):149–160.
2. Pain Management Guideline Panel. Clinicians’ quick reference guide to postoperative pain management in adults. Agency for Health Care Policy and Research, US Department of Health and Human Services. *J Pain Symptom Manage*. 1992;7(4):214–228.
3. American Society of Anesthesiologists Task Force on Acute Pain Management. Practice guidelines for acute pain management in the perioperative setting: an updated report by the American Society of Anesthesiologists Task Force on Acute Pain Management. *Anesthesiology*. 2012;116(2):248–273.
4. The Management of Postoperative Pain Working Group [webpage on the Internet]. VHA/DoD Clinical Practice Guideline for the Management of Postoperative Pain; 2002. [updated May, 2002]. Available from: http://www.healthquality.va.gov/guidelines/Pain/pop/. Accessed September 18, 2014.
5. The Joint Commission [webpage on the Internet]. Facts About Pain Management; 2012. [updated January 9, 2012]. Available from: http://www.jointcommission.org/pain_management/. Accessed October 15, 2014.
6. American Pain Society [webpage on the Internet]. Pain Care Coalition; 2016. Available from: http://www.americanpain society.org/get-involved/pain-care-coalition. Accessed March 11, 2016.
7. Adamson RT, Lew J, Bejarov E, Amara S, Rezai J. Clinical and economic impact of intra- and postoperative use of opioids and analgesic devices. *Hosp Pharm*. 2011;46(6 suppl 1):S1–S3.
8. Oderda GM, Said Q, Evans RS, et al. Opioid-related adverse drug events in surgical hospitalizations: impact on costs and length of stay. *Ann Pharmacother*. 2007;41(3):400–407.
9. Oderda G. Challenges in the management of acute postsurgical pain. *Pharmaco therapy*. 2012;32(9 pt 2):6S–11S.
10. Wheeler M, Oderda GM, Ashburn MA, Lipman AG. Adverse events associated with postoperative opioid analgesia: a systematic review. *J Pain*. 2002;3(3):159–180.
11. Goetsch WG, Sukel MP, van de Peer DL, van Riemsdijk MM, Herings RM. In-hospital use of opioids increases rate of coded postoperative paralytic ileus. *Pharmacoepidemiol Drug Saf*. 2007;16(6):668–674.
12. Senagore AJ. Pathogenesis and clinical and economic consequences of postoperative ileus. *Am J Health Syst Pharm*. 2007;64(20 suppl 3):S3–S7.
13. Exparel [Prescribing Information]. Parsippany, NJ: Pacira Pharmaceuticals, Inc.; 2015.
14. Viscusi ER, Sinatra R, Oncel E, Ramamoorthy SL. The safety of liposome bupivacaine, a novel local analgesic formulation. *Clin J Pain*. 2014;30(2):102–110.
15. Dasta J, Ramamoorthy S, Patou G, Sinatra R. Bupivacaine liposome injectable suspension compared with bupivacaine HCl for the reduction of opioid burden in the postsurgical setting. *Curr Med Res Opin*. 2012;28(10):1609–1615.
16. Cohen SM, Vogel JD, Marcet JE, Candiotti K. Liposome bupivacaine for improvement in economic outcomes and opioid burden in GI surgery: IMPROVE study pooled analysis. *J Pain Res*. 2014;7:359–366.
17. Morales R Jr, Menz H 3rd, Newall G, Patronella C, Masters O 3rd. Use of abdominal field block injections with liposomal bupivacaine to control postoperative pain after abdominoplasty. *Aesthet Surg J*. 2013;33(8):1148–1153.
18. Hutchins J, Vogel RJ, Ghebre R, et al. Ultrasound-guided subcostal transversus abdominis plane infiltration with liposomal bupivacaine for patients undergoing robotic-assisted hysterectomy: a retrospective study. *Int J Gynecol Cancer*. 2015;25(5):937–941.
19. Feierman DE, Kronenfeld M, Gupta PM, Younger N, Logvinskiy E. Liposomal bupivacaine infiltration into the transversus abdominis plane for postsurgical analgesia in open abdominal umbilical hernia repair: results from a cohort of 13 patients. *J Pain Res*. 2014;7:477–482.
20. Sternlicht A, Shapiro M, Robelen G, Vellayappan U, Tuerk IA. Infiltration of liposome bupivacaine into the transversus abdominis plane for postsurgical analgesia in robotic laparoscopic prostatectomy: a pilot study. *Local Reg Anesth*. 2014;7:69–74.
21. U.S. Department of Health and Human Services [webpage on the Internet]. Quality Improvement Activities FAQs; 2015. [updated 2015]. Available from: http://www.hhs.gov/ohrp/policy/faq/quality-improvement-activities/. Accessed January 20, 2015.
22. Kvolik S, Kristek J, Sakic K, Takac I, Gulam D. A wound infiltration as a method of postoperative analgesia. *Period Biol*. 2009;111(2):241–246.
23. Taylor R Jr, Pergolizzi JV, Sinclair A, et al. Transversus abdominis plane infiltration with liposomal bupivacaine for patients undergoing robotic-assisted hysterectomy: a retrospective study. *Ann Pharmacother*. 2013;47(4):332–344.
24. Johns N, O’Neill S, Venthant NT, Barron F, Brady RR, Daniel T. Clinical effectiveness of transversus abdominis plane (TAP) block in abdominal surgery: a systematic review and meta-analysis. *Colorectal Dis*. 2012;14(10):e635–e642.
25. Rafi AN. Abdominal field block: a new approach via the lumbar triangle. *Anaesthesia*. 2001;56(10):1024–1026.
26. Petersen PL, Mathiesen O, Torup H, Dahl JB. The transversus abdominis plane block: a valuable option for postoperative analgesia? A topical review. Acta Anaesthesiol Scand. 2010;54(5):529–535.

27. Jankovic Z. Transversus abdominis plane block: the Holy Grail of anaesthesia for (lower) abdominal surgery. Period Biol. 2009;111(2):203–208.

28. Findlay JM, Ashraf SQ, Congahan P. Transversus abdominis plane (TAP) blocks: a review. Surgeon. 2012;10(6):361–367.

29. Gupta A. Wound infiltration with local anaesthetics in ambulatory surgery. Curr Opin Anaesthesiol. 2010;23(6):708–713.

30. Ganapathy S, Brookes J, Bourne R. Local infiltration analgesia. Anesth Clin. 2011;29(2):329–342.

31. Scott NB. Wound infiltration for surgery. Anaesthesia. 2010;65(suppl 1):67–75.

32. Mukhtar K. Transversus abdominis plane (TAP) block. J NY School Reg Anesthesia. 2009;12:28–33.

33. Rawal N. Epidural technique for postoperative pain: gold standard no more? Reg Anesth Pain Med. 2012;37(3):310–317.

34. Marret E, Remy C, Bonnet F. Meta-analysis of epidural analgesia versus parenteral opioid analgesia after colorectal surgery. Br J Surg. 2007;94(6):665–673.

35. Rigg JR, Jamrozik K, Myles PS, et al; MASTER Anaesthesia Trial Study Group. Epidural anaesthesia and analgesia and outcome of major surgery: a randomised trial. Lancet. 2002;359(9314):1276–1282.

36. De Lorimier R. New Opportunities for Hospitals to Improve Economic Efficiency and Patient Outcomes: The case of EXPAREL™, a long-acting, non-opioid local analgesic. Mountain View, CA: Frost and Sullivan; 2011.

37. Cohen SM. Extended pain relief trial utilizing infiltration of Exparel®, a long-acting multivesicular liposome formulation of bupivacaine: a Phase IV health economic trial in adult patients undergoing open colectomy. J Pain Res. 2012;5:567–572.

38. Candidotti KA, Sands LR, Lee E, et al. Liposome bupivacaine for postsurgical analgesia in adult patients undergoing laparoscopic colectomy: results from prospective phase IV sequential cohort studies assessing health economic outcomes. Curr Ther Res. 2014;76:1–6.

39. Vogel JD. 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. J Pain Res. 2013;6:605–610.

40. 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;6:549–555.

41. CPT codes. American Medical Association. Available from: http://coder.aapc.com/cpt-codes/. Accessed April 4, 2016.