# PREVENTING LOCAL ANESTHETIC SYSTEMIC TOXICITY ASSOCIATED WITH LIPOSOMAL BUPIVACAINE USE

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## Dedication

This one's for you, Dad. I liked to tease you that I wanted to be the first Dr. Althof in the family when you discussed pursuing your doctorate in education. However, I'm proud to say that you were the first, and I will proudly follow in your footsteps to become the second Dr. Althof. I say that I am never going back to school, and thus why I chose to pursue a terminal degree; but alas, your lifelong love of learning was engrained upon me and I'm already envisioning the Spanish classes I want to take once I'm bored of being out of school for a while. I wish you were still here earthside to celebrate with us all. (For anyone struggling with their mental health, help is available, and life can get better. Your people want you here. For those struggling with thoughts of suicide, please call or text 988 for free support.)

To my lovely husband, Brendan, thank you for your support throughout these three years. I appreciate every dinner made, lunch packed, and chore completed around the house to take the pressure off of me. Thanks for always being willing to quiz me before a test and listening to my crazy healthcare stories. I can't wait to celebrate this journey being DONE with you by my side. Let's go have some fun!!!

Shiloh and Wilbur, thanks for always being the sweetest boys a girl could have. Shiloh, you've been the best dissertation writing buddy for both my dad and me. We couldn't have done it without you laying by our sides. Wilbur, keep being the precious baby of the family. I love you both so much.

To my family and friends, I can't wait to have a reliable schedule to be able to spend more time with all of you without the stress of school lingering in the back of my mind. Thanks for the fun adventures shared, and I can't wait to make new memories with you all!

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## Abstract

**Background:** Local anesthetic administration has become an integral part of pain management in the perioperative setting. However, all local anesthetics have the potential for causing local anesthetic systemic toxicity (LAST), a condition that may result in patient morbidity and mortality. Novel formulations of local anesthetics, such as long-acting liposomal bupivacaine (Exparel®), have the potential to cause or contribute to LAST development over 96 hours past administration. Anesthesia providers must be vigilant about the risks of administration of additional local anesthetics when a patient has received Exparel®. **Purpose:** To reduce the incidence of accidental LAST in patients treated with Exparel® at a southeastern urban hospital. **Methods:** Anesthesia providers at the study hospital received an educational presentation reviewing Exparel®'s pharmacology, LAST signs/symptoms, and LAST treatment. **Results:** Twenty-five (n = 25) anesthesia providers participated in a pre- and post-educational presentation test, with a statistically significant rise in test scores. Despite a measurable increase in provider knowledge regarding the risks and consequences of administration of additional local anesthetics following Exparel® administration, this did not result in a decrease in the administration of local anesthetics with Exparel®. **Conclusion and Recommendations:** Anesthesia providers should remain ever vigilant of LAST risks and an educational session about Exparel® and LAST can help providers review best practices in prevention and treatment. The implementation of an intraoperative alert in the electronic medical record to notify anesthesia providers of the prior administration of Exparel® could further reduce the incidence of local anesthetic administration during the period of increased risk of LAST. Further studies investigating Exparel® and other local anesthetic use should be conducted to advance our

knowledge on their use and toxicities. **Key Words:** liposomal bupivacaine, Exparel®, local anesthetic systemic toxicity, LAST.

## Background and Significance

Local anesthetics are frequently utilized in perioperative medicine to prevent and treat pain both during and after surgery. Local anesthetics may be administered intravenously, through infiltration, neuraxial anesthesia, or via a peripheral nerve block (Lirk et al., 2018). While they are useful, the administration of local anesthetics comes with serious potential risks. Local anesthetic systemic toxicity (LAST) is a rare but serious condition that can cause deadly cardiovascular and neurologic side effects when toxic serum levels of local anesthetics occur (Neal et al., 2018). Local anesthetics' potentially toxic doses are also cumulative; thus, the provider must consider all possible sources and doses of local anesthetic the patient has received prior to administering additional local anesthetic agents (Rosenberg et al., 2004). Novel local anesthetic formulations, such as liposomal bupivacaine (Exparel®), have been developed to provide the patient with a steady serum level of local anesthetic over a 96-hour time period (Pacira Pharmaceuticals, 2023). During this interval, additional local anesthetic administration may lead to LAST (Pacira Pharmaceuticals, 2023).

At a southeastern urban level 1 trauma center, trauma patients admitted to the hospital often require surgical intervention, with the potential need for multiple surgeries from various specialties. If the patient initially presents for an exploratory laparotomy with the general surgery team and receives liposomal bupivacaine from the surgeon via infiltration of the tissues, the patient should not receive additional local anesthetic for the next 96 hours per Exparel®'s usage guidelines (Pacira Pharmaceutical, 2023). To prevent unintentional LAST, an Exparel®

wristband is typically applied to the patient. Additionally, a reference document is placed in the chart and Exparel® administration is documented in the electronic medical record. However, if the wristband is removed to start a new IV, the paper falls out of the chart, or the anesthesia provider doesn't take the time to review the patient's electronic medical record in search of prior medications administered, they may be unaware that the patient should not receive any more local anesthetic. In this case, the patient may accidentally experience a local anesthetic overdose. Symptoms of LAST may develop, resulting in increased patient morbidity and mortality. In a six-month time period, from May 3, 2022, to November 2, 2022, 2,713 patients received liposomal bupivacaine at this southeastern urban hospital. To prevent LAST from occurring in patients who have received Exparel®, I planned to educate anesthesia providers about Exparel® and implement a best practice alert within the southeastern urban hospital's electronic medical record system, Epic. This alert will flag the intraoperative anesthetic chart and alert the anesthesia provider when the patient has received liposomal bupivacaine in the past 96 hours and should not receive any additional local anesthetic agents.

## Purpose

The purpose of this project is to reduce the incidence of accidental local anesthetic systemic toxicity in patients treated with liposomal bupivacaine (Exparel®) at a southeastern urban hospital.

## Review of Current Evidence

A literature search was conducted including queries of the following databases: PubMed, the Cumulated Index of Nursing and Allied Health Literature (CINAHL), Ovid, Proquest, and Google Scholar. Search terms included: local anesthetic, local anesthetic systemic toxicity, Exparel®, liposomal bupivacaine, local anesthetic systemic toxicity prevention, local anesthetic maximum doses, and local anesthetic safety. Exclusion criteria included articles not written in English, published outside the United States, and not about human subjects.

Local anesthetic drugs were first noted for their numbing properties in the 1800s. In 1892, Einhorn synthesized procaine, the first of several local anesthetic agents now used in daily anesthesia practice (Harmatz, 2009). Local anesthetics are useful in anesthesia practice, due to their ability to block action potentials at sodium channels and prevent nerve conduction of pain, sensory or motor signals (Arumugam et al., 2020). However, their use carries risks. The most lethal potential side effect is local anesthetic systemic toxicity which can lead to neurologic and cardiovascular side effects, including seizures, cardiac dysrhythmias, and death (Neal et al., 2018). As is the case with any medication, the dose given must be large enough to have the intended effect of neural blockade, but small enough to limit undesirable side effects (Mather et al., 2015).

In current anesthesia practice, local anesthetics have numerous applications, and are utilized by a variety of perioperative providers (Neal et al., 2018). The patient may initially receive a topical anesthetic from the pre-operative nurse before their intravenous catheter is placed (Arumugam et al., 2020). An anesthesia provider may place a peripheral nerve block, such as an interscalene brachial plexus block, prior to surgery to control post-operative pain with both an immediate acting local agent, like bupivacaine, and the newest local anesthetic on the

market: a long acting, slow-release liposomal bupivacaine (Pacira Pharmaceuticals, 2023). The patient may receive a spinal arachnoid block from an anesthesia provider to prevent sensory and motor transmission during the surgery (Neal et al., 2018). Surgeons may choose to inject local anesthetic at the site of incision to prevent incisional pain and limit autonomic sympathetic responses (Arumugam et al., 2020). During the induction of anesthesia, anesthesia providers may inject intravenous lidocaine to prevent the burning sensation of propofol administration. Local anesthetics are useful medications for preventing perioperative pain. They can also be used for sensory and motor blockade. Anesthesia providers must remain cognizant of the maximum recommended doses of local anesthetic drugs, and when, where, and how much a patient has received to prevent LAST.

At the project site, there have been several instances of potential adverse events related to the use of local anesthetics. It is not uncommon for a surgeon to inquire how much local anesthetic the patient can safely receive. With the introduction of liposomal bupivacaine in 2012, anesthesia providers welcomed a novel long-acting local anesthetic (Pacira Pharmaceuticals, 2023). However, Exparel® also contributes to the risk of LAST for up to 96 hours following its administration (Pacira Pharmaceuticals, 2023).

In an eight-week time period, from May 24, 2023, to July 19, 2023, 122 patients received liposomal bupivacaine at this southeastern urban hospital. During this same time frame, 76 of the 122 patients received lidocaine and 1 patient received ropivacaine in addition to liposomal bupivacaine (see Appendix A). According to Pacira Pharmaceuticals' (2023) prescription guidelines, additional use of any local anesthetics should be avoided for 96 hours after Exparel® administration to prevent inadvertent LAST. By implementing an intraoperative best practice alert in the electronic medical record (EMR), Epic, anesthesia providers will be notified anytime

a patient has received Exparel® in the previous 96 hours. With the implementation of Exparel® education for anesthesia providers, they will know the patient should not receive additional local anesthetic agents when a patient has had Exparel®.

**Local Anesthetic Maximum Dosing: The Evidence (Or Lack Thereof)**

The current recommended maximum doses of local anesthetics are agent and route specific but are not based on studies in human subjects (Rosenberg et al., 2004). Rather, the maximum dose of all local anesthetics is extrapolated from animal studies, measured blood concentrations of local anesthetic after use in clinical experiences, pharmacokinetic – pharmacodynamic studies, and case studies of local anesthetic systemic toxicity in human patients (Rosenberg et al., 2004). Data extrapolated from animal studies to estimate the maximum safe dose in humans is inadequate and maximum allowable doses are most likely underestimated in humans (Moore et al., 1977). This can lead to underdosing that prevents the local anesthetic from providing sufficient sensory and/or motor blockade (Moore et al., 1977). Toxic doses of local anesthetics were originally determined via animal studies. It would be unethical to subject a human to the potentially deadly central nervous system and cardiovascular effects of large toxic doses of local anesthetics to determine toxic doses in human subjects (Mather et al., 2005). Some maximum doses, such as that for bupivacaine, are unsubstantiated and contradict animal studies showing higher potency, which should equate to a lower maximum dose than currently recommended (Rosenberg et al., 2004). There is also no evidence supporting increased dosing recommendations when epinephrine is added to local solution (Rosenberg et al., 2004). Ideally, more research should be done to determine safe, effective dosing of local

anesthetic in humans; however, the potential for deadly complications preclude conduction of these studies (Kant et al., 2013).

The effective dose, or $ED_{95}$, is a clinically relevant and important dosing standard, as 95% of patients will have the desired effect of the drug after receiving the $ED_{95}$ dose (Kant, 2013). Up and down methodology in anesthesia allows for designing experiments to measure responses at any point along the dose-response curve, with commonly targeted points resembling the effective dose in 50% of patients ($ED_{50}$), 95% of patients ($ED_{95}$), or 99% of patients ($ED_{99}$) of a drug, all while utilizing a small sample size and statistical analysis to determine safe, effective doses (Pace & Stylianou, 2007). Up and down methodology was first utilized in anesthesia for determining the effective dose of inhalation agents and has since been applied to numerous medications commonly used in anesthetic practice (Pace & Stylianou, 2007). With up and down methodology, the researcher determines a dosing level, sample size of patients from the target population, and the definition of a positive response to the drug. Once chosen, the first patient receives a dose, and depending on their response, the dose is updated either up, for a negative or lack of response, or down, for a positive effective response (Pace & Stylianou, 2007).

Another method of determining the $ED_{95}$ of local anesthetics is the continual reassessment method. In Kant et al.'s (2013) study of the application of the continual reassessment method, they researched the $ED_{95}$ of 0.5% bupivacaine for ultrasound-guided supraclavicular blocks. Kant et al. (2013) determined this method resulted in a tight confidence interval with a low sample size, and recommended this method be applied in future studies concerning $ED_{95}$ dosing. The continual reassessment method is best utilized when estimating the $ED_{95}$ or the $ED_{99}$, as these values require precision, something up and down methodology lacks (Kant et al., 2013). Since there is potential for harm in testing maximal doses of local anesthetic

in human subjects, it would be unethical to subject human research participants to a risk of LAST from local anesthetic dosing experiments. Both the continual reassessment method and up and down methodology are strategies for testing local anesthetic agent maximal dosing that can prevent participant harm while contributing to maximum local anesthetic dosing knowledge.

**Patient Specific, Multi-factorial Dosing of Local Anesthetic**

When administering local anesthetics, it is important to consider the patient's age, comorbidities, risk versus benefit, and current medications, as these can all influence the risk of toxicity (Harmatz, 2009). Local anesthetics appear in the central circulation once taken up by vascular tissues. When this occurs, there are multiple scenarios in which the threshold for toxicity can occur: local anesthetic overdose relative to patient weight, metabolizing capacity, plasma protein concentration, or injection site perfusion, accidental intra-arterial injection, or accidental intravascular injection (Lirk et al., 2018). Liposomal bupivacaine is designed to maintain a steady serum plasma concentration of bupivacaine for up to 96 hours (Pacira Pharmaceuticals, 2023). The liposomes in Exparel®, which are designed to release bupivacaine slowly over time, may also inadvertently burst and release a potentially toxic bolus of bupivacaine if exposed to local anesthetics other than bupivacaine (Pacira Pharmaceuticals, 2023).

Studies of local anesthetic administration in large animals can be used to estimate the pharmacokinetic and pharmacodynamic effects of the drugs in humans (Mather at el., 2005). Rosenberg et al. (2004) suggest providers individualize the maximum doses of local anesthetic for each patient and worry less about the defined maximum dose for the drug, given that it varies amongst countries and pharmaceutical companies. To consistently administer local anesthetic

safely, a provider must consider the site of injection, its vascularity, and the likelihood of local anesthetic binding to tissues (Rosenberg et al., 2004). Each local anesthetic has its own vasoactivity. Higher concentration solutions may vasodilate and speed up absorption, while lower concentration formulas or high-volume blocks may vasoconstrict or compress surrounding vessels, slowing systemic uptake (Rosenberg et al., 2004). Local anesthetic solutions containing epinephrine vasoconstrict surrounding vessels, slowing systemic absorption, and prolonging neural blockade. However, epinephrine is inappropriate for use in extremely vascular tissue susceptible to necrosis from vasoconstriction (Rosenberg et al., 2004). A patient's age is also important; as age increases, clearance of local anesthetics generally declines due to deteriorating blood flow and organ dysfunction (Rosenberg et al., 2004). Patients with renal dysfunction are prone to enhanced initial absorption due to hyperdynamic circulation from uremia, leading to high peak plasma levels and a reduction in clearance of the drug (Rosenberg et al., 2004). For those with hepatic dysfunction, decreased doses of amide local anesthetics should be used, particularly with continuous infusions or repeated blocks, to account for reduced clearance (Rosenberg et al., 2004). In patients with severe heart failure, doses should be decreased, as clearance will be reduced due to decreased hepatic and renal blood flow; in contrast, cerebral blood flow is typically unchanged due to autoregulation, leaving the patient vulnerable to central nervous system toxicity (Rosenberg et al., 2004). During pregnancy, increased cardiac output, progesterone induced sensitivity of nerve axons to neural blockade, and decreased protein binding all contribute to potential toxicity (Rosenberg et al., 2004). Lastly, a patient's medication list should be reviewed for drug-drug interactions. Some medications, such as fluvoxamine or itraconazole, inhibit liver enzymes that normally metabolize local anesthetics, increasing the risk of local anesthetic toxicity (Rosenberg et al., 2004).

A single maximum dose of local anesthetic is stated for all local anesthetics, despite different absorptive capacities at different sites throughout the body (Moore et al., 1977). In Moore et al.'s (1977) review of anesthetic records over the course of nearly a decade, eight out of 9287 patients developed local anesthetic systemic toxicity, all resulting from inadvertent intravascular injection. The doses used during these injections were less than the recommended maximum doses for the drugs. Local anesthetic injection into the subcutaneous layer or around the femoral nerve will have the lowest systemic absorption, while intercostal or tracheal administration will have the highest absorption and risk of provoking LAST (Mather et al., 2005). It is reasonable to propose local anesthetic doses be based on the site of injection versus agent given, although this does not account for the ever-present risk of accidental intravascular injection and local anesthetic systemic toxicity (Mather et al., 2005).

**Safeguards to Protect Patients from Local Anesthetic Systemic Toxicity**

Prevention of local anesthetic systemic toxicity must involve several safeguards. This includes better communication among the entire surgical and anesthesia teams to prevent inadvertent local anesthetic overdose (Viderman et al., 2021). To facilitate accurate, complete communication, a time-out checklist should be performed prior to any local anesthetic administration. The checklist should include the name of the local anesthetic, the dose, time, and route given (AQI-AIRS Steering Committee, 2018). All team members should feel empowered to speak up when they encounter a patient safety concern, without fear of retribution (Umoren et al., 2022). Utilizing an integrated electronic medical record with the ability to track and flag when drugs are administered may help prevent duplicate orders or procedures (AQI-AIRS Steering Committee, 2018). However, this may be limited in the way orders are carried out in the operating room. Typically, no physical order or electronic entry occurs until after the medication

has already been administered. One way to prevent local anesthetic overdose is to have only the maximum allowable dose for the patient available on the surgical field. In this way, the surgical staff must confirm with the anesthesia staff the correct maximum allowable dose of the desired local anesthetic (AQI-AIRS Steering Committee, 2018). A time-out specifically including information about the use of Exparel® and confirmation of avoidance of other local anesthetics can help prevent LAST (Ilfeld et al., 2015). Limiting who can write orders in the post-anesthesia care unit (either the anesthesia team or the surgical service) may also help prevent duplicate or conflicting orders that would inadvertently overdose the patient with local anesthetic (AQI-AIRS Steering Committee, 2018). Prior to regional anesthesia techniques, informed consent discussions with the patient should include information about the risks, benefits, perioperative course, alternative options, and the general nature of the procedure (Benhamou et al., 2010). Finally, using web-based systems to track incidents that lead to poor outcomes or sentinel events may help guide future safe practice (Benhamou et al., 2010).

**Evidential Conclusions**

Local anesthetics are widely utilized in the anesthetic and perioperative setting to increase patient comfort; however, local anesthetic systemic toxicity is always a risk. Dosing recommendations for local anesthetics are generally based upon animal studies, up and down methodology, continual reassessment, and case reports in human subjects. When administering local anesthetics, providers should limit doses to the lowest effective dose to minimize risk of toxicity. Providers must be cognizant of the risks of local anesthetics related to administration site, an individual's comorbidities, and previously or concurrently administered medications. To

protect the patient, multiple safe checks should be implemented with each planned local anesthetic administration.

## Theoretical Model

Lewin's Theory of Planned Change is a 3-step process used to guide leaders in creating positive change (Hussain, Lei, et al., 2018). In the first step, unfreezing, the leader must identify driving and restraining forces in the individual, as well as the organization, to understand forces that must be amplified or mitigated to introduce change. The leader identifies a problem, illuminates the current vs. the desired outcome, and creates buzz over a potential solution within their organization (Shirey, 2013). In the second step, moving or transitioning, the leader enacts change. This step can be anxiety-provoking for organization members, as fear of the unknown and transformation occurs. Clear, frequent communication and education about the change may help to ease into the transition (Umoren et al., 2022). In the third step, refreezing, the change is made permanent (Shirey, 2013). Continued reappraisal of driving and restraining forces must occur to ensure the change becomes the "new norm" (Shirey, 2013).

Modeling Lewin's Theory of Planned Change, I have identified a problem within the southeastern urban hospital. Patients are being exposed to additional local anesthetic after receiving Exparel®, putting them at risk for LAST (Pacira Pharmaceuticals, 2023). In the second step, I will enact change by enabling a best practice alert within Epic and educating anesthesia providers about Exparel®. A co-administered education component for anesthesia providers will ensure they recognize why it is important to avoid additional local anesthetic administration with Exparel®. In the third step, I will reinforce the necessity in prevention of LAST following Exparel® administration with continued reappraisal of electronic medical records tracking the incidence of local anesthetic administration with Exparel® administration during a patient's hospital stay.

# Methods

## Design

I implemented a quality improvement project at a southeastern urban hospital in pursuit of preventing local anesthetic systemic toxicity following Exparel® use. My project was born during assigned clinical hours, as I witnessed a discussion in the break room amongst anesthesia providers at this hospital about the use of Exparel® and other local anesthetics. They wondered about the appropriate timeframe to administer multiple local anesthetics and the safety of giving other local anesthetics with Exparel® use. I saw an opportunity to increase anesthesia provider knowledge of safe Exparel® use with the goal of preventing deadly local anesthetic systemic toxicity.

To prevent the frequency of LAST, I planned to implement an intraoperative alert within Epic, the hospital's electronic medical record system, and an educational session for anesthesia providers about Exparel®. However, during the project implementation, the Epic team and I were unable to build a suitable intraoperative alert utilizing data pulled from the electronic medication administration record. Therefore, I pivoted to focusing solely on the educational session with anesthesia providers regarding Exparel® and the risk of LAST. A presentation was given during the anesthesia providers' monthly meeting, which included participation by physician anesthesiologists, certified registered nurse anesthetists, and anesthesiologist assistants (see Appendix D). An identical pre-test and post-test were administered anonymously to a total of 25 participants (see Appendix B). Data from counts of patients who received Exparel® or Exparel® plus additional local anesthetics was collected both before and after the intervention to estimate

whether a change in provider actions had occurred. The pre-tests and post-tests were also analyzed to determine if the educational session influenced providers' knowledge of Exparel®.

**Permissions**

The University of North Carolina at Greensboro's Institutional Review Board was consulted on and approved this project. Patient data was protected and not used during this project, as only a count of the number of patients receiving Exparel® was used, withholding all patient identifying information. Anesthesia providers participating in the educational session were also protected, as no personal identifying or demographic information was collected from participants. The project site also provided permission for this project.

**Translational Framework**

The plan-do-study-act (PDSA) method of enacting quality improvement projects is a cyclic framework for clinicians to follow to implement positive change in the healthcare environment (Taylor et al., 2014). In the plan stage, the healthcare provider identifies a need for change to improve practice. In this case, I identified the need for additional safeguards regarding the use of liposomal bupivacaine, particularly in patients who may receive serial procedures or multiple surgeries within a few days. To improve a process, the clinician must then identify team members willing to enact change who understand the current issue. I planned to work with anesthesia providers at a southeastern urban hospital to create positive change. I planned to administer a pre-intervention and post-intervention questionnaire assessing providers' knowledge of Exparel®. I originally planned to also implement an alert within Epic to notify anesthesia

providers when a patient had Exparel®. Once the team had been assembled, I could create an action plan to carry out in step 2: Do.

Once the planning stage was complete, the next step in PDSA involved carrying out the implementation of the change. For this project, I planned to create an alert in Epic that populated in the intraoperative tab to warn anesthesia providers when the patient had received Exparel® in the past 96 hours. Unfortunately, this planned piece of the project was unable to be implemented. I was able to successfully provide an educational session for anesthesia providers about Exparel®. The intervention included a PowerPoint presentation reviewing Exparel®'s pharmacology, approved uses and doses, and prevention and treatment of LAST. Whenever Exparel® is given, the current protocol is for the medication to be charted in the Epic medication administration record (MAR), a paper placed in the paper chart with the time/date/amount of medication received, and for a blue Exparel® wristband to be placed on the patient's wrist, only to be removed once the 96 hours post-administration have passed. However, it is not uncommon for the Exparel® wristband to be either inadvertently or purposefully removed for the purpose of starting a new IV or arterial line in the wrist. In this case, the clinician must rely on taking the time to look in the paper chart or searching through past MAR records. This can prove unreliable and/or time-consuming. With an Epic alert built into the chart, the anesthesia provider would have an easy way of identifying which patients should not receive more local anesthetic perioperatively.

Once the change has been implemented, the next step is to study the effects. I identified the percentage of patients who received another local anesthetic in addition to Exparel® dosing both before the intervention and after. Ideally, zero patients will receive any additional local anesthetics after receiving Exparel® for at least 96 hours post-injection. If this percentage

declined after the intervention and anesthesia providers were more knowledgeable about local anesthetic dosing to prevent LAST, then it will have been effective.

The last step in the process, act, refers to long term outcomes. If the intervention was successful, with few to no unintended consequences, the change can be standardized and implemented for good, or perhaps across other hospitals. If the change did not improve outcomes, then the team can look at other approaches that may prove to be more successful.

**Setting**

This project was conducted at a not-for-profit, public southeastern urban hospital in the United States. This hospital is the only level 1 trauma center in the city and is licensed for 567 acute care beds. For fiscal year 2021, 7,927 inpatient surgeries, 10,307 outpatient surgeries, and 6,444 endoscopies were performed at this institution. These calculations do not include any obstetrical visits or other procedures in which anesthesia or local anesthetic use may have been involved.

**Sample**

Using the electronic medical records in Epic, I first identified any patients that received Exparel® during their anesthesia encounter for an eight-week time period before the intervention. After obtaining this number, I further narrowed the search criteria to include patients who have received both Exparel®, plus any of the following local anesthetics during their hospital encounter: lidocaine, lidocaine with epinephrine, ropivacaine, chloroprocaine, or benzocaine. Bupivacaine was excluded from the search criteria, as it is permissible to mix bupivacaine with Exparel® upon initial administration (Pacira Pharmaceuticals, 2023). While other local

anesthetics exist, they are not within this hospital's pharmaceutical formulary available for clinician use, and therefore will not be included. The sample included all patients with an anesthesia encounter who received these medications, regardless of age, gender, ethnicity, or any additional patient demographics. After the intervention was implemented, I again performed the same search within Epic with the same criteria to determine if the percentage of patients exposed to additional local anesthetic declined.

At this southeastern level 1 trauma center, there are certified registered nurse anesthetists (CRNAs), physician anesthesiologists, and anesthesiologist assistants (AAs) employed. All anesthesia providers were invited to participate in the educational session on preventing LAST with Exparel® that took place during the required monthly department meeting. A questionnaire assessing the knowledge of anesthesia providers was given both pre-educational session and post-educational session. No personal identifying information was collected from participants.

**Project Implementation**

I planned to collaborate with anesthesia providers and Epic software designers at the southeastern urban hospital to incorporate my quality improvement project. A best practice alert would have needed to be created by the Epic team members that would flag in the intraoperative section of the anesthesia workflow chart. I envisioned this alert automatically showing for any patients that had Exparel® charted in their MAR in the past 96 hours. If it had been greater than 96 hours since administration, the alert would drop off the page and no longer show. After communicating with the Epic team members regarding an alert of this nature, we were unable to construct a suitable alert within the chart.

I was able to successfully provide an educational session on Exparel® for anesthesia providers at the southeastern urban hospital (see Appendix D). The presentation addressed Exparel®'s pharmacology, current practices in place for documentation of Exparel® administration, and an overview of local anesthetic systemic toxicity (LAST) symptoms and treatment. A questionnaire was provided both pre-education and post-educational session to assess for gaps in knowledge related to Exparel® use and the risk of LAST, hopefully filled by the educational session (see Appendix B for pre-test distributed to participants). Appendix C contains the correct answers to the pre-test/post-test, noted in red font. Participants received a stapled numbered packet, with the first page consisting of the pre-test, and the second page consisting of the identical post-test. Participants were instructed to grab a test before the presentation and answer the pre-test before the presentation began. At the conclusion of the presentation and discussion that followed, participants were asked to complete the post-test and hand in their completed tests. No personal identifying information was collected from participants. Pre-tests and post-tests were each uniquely numbered, so if a set was separated, the participant's corresponding tests could still be matched.

**Data Collection**

Data collection ensured the privacy of all patients counted in my sample, as no patient identifying information was used or looked at for data. The data collected was simply a count of the number of patients with defined characteristics. Data collection occurred for eight weeks pre-intervention and four weeks post-intervention for comparative data analysis. For eight weeks prior to my intervention, I collected data from the electronic medical records system in use at the southeastern urban hospital with the assistance of the hospital's chief certified registered nurse

anesthetist. The first set of data included a filter to determine the total number of patients who received Exparel® in the hospital during an anesthesia encounter from May 24th of 2023 to July 19th of 2023. This data set was then further filtered to determine the number of patients who received Exparel® in addition to lidocaine, lidocaine with epinephrine, ropivacaine, chloroprocaine, and benzocaine (see Appendix A). While additional local anesthetics do exist, these were all of the local anesthetics available for use at this hospital at the time of project implementation. The sample included all patients with an anesthesia encounter who received these medications, regardless of age, gender, ethnicity, or any additional patient demographics. Bupivacaine was excluded from the search criteria, as it is permissible to co-administer bupivacaine with Exparel® (Pacira Pharmaceuticals, 2022). Once the educational session intervention was implemented on January 5th of 2024, I gathered an additional four weeks of data post-intervention from January 5th of 2024 to February 2nd of 2024 (see Appendix E).

Data collected from the anesthesia provider questionnaire did not include any personal identifying information. Participants were unknown to me prior to presenting and randomly entered the conference room and grabbed a test packet prior to the presentation. Pre-tests and post-tests were stapled and matched according to a number given on both papers, so data was able to be matched and compared from individual responses. A total of twenty-five matching pre-tests and post-tests were completed and collected (n = 25). The sample included physician anesthesiologists, certified registered nurse anesthetists, and anesthesiologist assistants employed at the southeastern urban hospital who attended the educational session about Exparel®. Data from these tests was entered in Excel for analysis. Pre-tests and post-tests were scored according to the answers provided in Appendix C. Both individual question responses and total test results were recorded for analysis.

## Data Analysis

Data analysis was completed via Microsoft Excel. A total of twenty-five matching pre-tests and post-tests were collected and entered into Excel for data analysis. The tests contained 5 questions, and each question answered correctly was given 1 point, for a total of 5 points possible if participants answered all questions correctly. Score totals for both pre-tests and post-tests were tallied as well as individual question scores to determine if one or more questions may have been more frequently missed. A paired t-test was performed on the total scores in conjunction with a statistician employed by the University of North Carolina at Greensboro (see Appendix F).

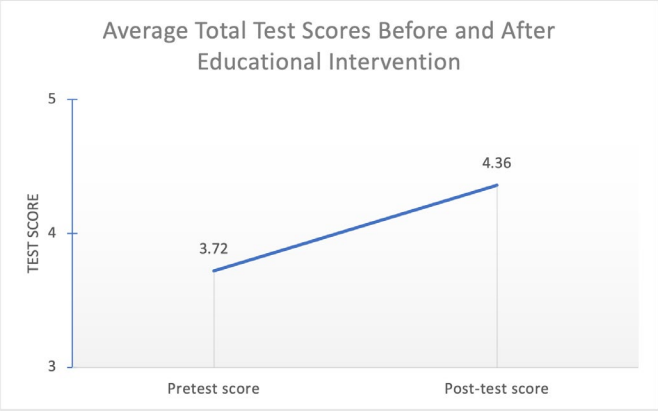
Data collected from Epic was also entered into Excel for the purpose of comparison. Due to time constraints of this project, eight weeks of data was collected from Epic prior to the project's implementation, but only four weeks was collected after implementation. Because of this, only the percentage of patients who received Exparel versus Exparel plus another local anesthetic was compared.

## Results

A total of twenty-five participants attended the educational presentation on Exparel® and completed a pre-test and post-test (n=25). Data from these tests was entered in Excel for analysis. A paired sample of means t-test was performed on the total test scores and revealed a statistically significant ($p<0.05$, $p=0.0003$) increase in scores from before to after the educational session (see Appendix G). The mean test score increased from 3.72 points pre-test (SD 0.377) to 4.36 points post-test (SD 0.323). With a statistically significant increase in test scores after the

educational session, it is reasonable to conclude an educational session about Exparel® use and prevention of LAST can increase provider knowledge.

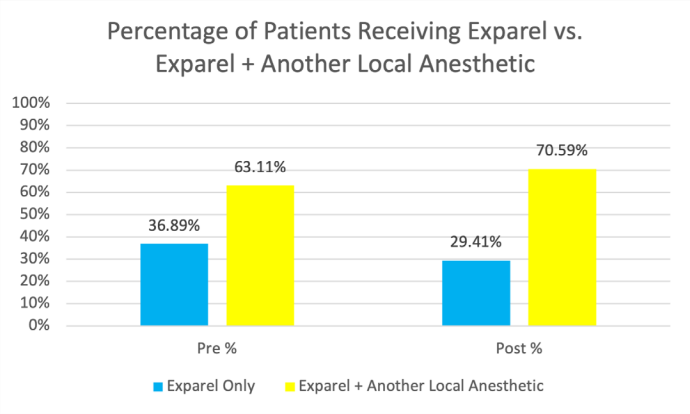
**Figure 1: Mean Test Scores**




While there was a statistically significant increase in mean test scores after the educational presentation, the percentage of patients who received Exparel® and additional local anesthetics did not follow expectations. Ideally, after education about preventing LAST with Exparel® use, anesthesia providers would ensure a patient did not receive any additional local anesthetics within 96 hours of administration of Exparel®. Thus, I expected a decline in the percentage of patients who received Exparel® plus additional local anesthetic. However, the opposite was true. Prior to administering the educational session, eight weeks of Epic data was collected (see Appendix A). A total of 122 patients received Exparel® during this time frame, of which 76 also received lidocaine and 1 patient received ropivacaine, for a total of 63.1% of patients potentially receiving an inappropriate local anesthetic dose. Epic data was again assessed for four weeks after the session, during which 51 patients in total received Exparel® (see Appendix F). During this time, 34 patients also received lidocaine and 2 patients received

ropivacaine, for a total of 70.6% of patients potentially receiving an inappropriate local anesthetic dose.

**Figure 2: Percentage of Patients Receiving Exparel vs. Exparel + Another Local Anesthetic**




An unexpected barrier during my project occurred when I was unable to implement the intraoperative alert within Epic. This altered the timeline of my project, as I continued to be in contact with the healthcare system's Epic team to come up with a solution. When it was determined we could not implement an alert as I had envisioned and I came upon the month I planned to be collecting post-implementation data, I shifted gears to solely implementing an educational session for anesthesia providers about Exparel®.

## Discussion

While the data analysis from the tests administered to anesthesia providers was statistically significant in increasing test scores after an educational session, I was unable to correlate a clinical improvement. Since Epic data showed the percentage of patients receiving other local anesthetics in additional to Exparel® actually increased from before to after the presentation, more complete data would need to be collected to correlate a decreased risk of

LAST with Exparel® use after education on the topic. An individual chart review was not performed for each patient identified as a recipient of liposomal bupivacaine. Therefore, it is not possible to conclude whether the addition of other local anesthetics was given in a timeframe prior to Exparel® administration or 96 hours or greater post-Exparel® administration. These patients could have been reasonably given other local anesthetics throughout their perioperative course and/or hospital stay. Alternatively, there could have been an inappropriately timed administration of local anesthetics contributing to the risk of LAST. Individual chart reviews of patients' electronic medication administration records would have to occur to determine the timing of medications given. A longer time period of data collection would have increased the number of data points and strengthened the conclusions of the statistical analysis.

During this project, the anesthesia group staffing this southeastern hospital was replaced. Subsequently, the majority of the staff that was present during the pre-implementation data was no longer employed within this facility post-implementation. The number of surgeries, and therefore anesthetic records, decreased after the new anesthesia group began employment in the fall of 2023. Therefore, it is possible there are differences in Epic data due to the different staff members employed or number and types of cases performed post-implementation.

During the educational presentation session, participants were offered the chance to ask questions or share their experiences with the group. One anesthesia provider asked if Exparel® was approved or being studied to be used with ropivacaine, the levorotatory enantiomer of bupivacaine (Kuthiala & Chaudhary, 2011). According to Pacira Pharmaceuticals' (2023) most recent prescribing information for Exparel®, bupivacaine remains the only local anesthetic with which Exparel® should be coadministered. I had not previously encountered any studies specifically designed to test Exparel® with ropivacaine and was not able to locate any after the

session. The anesthesia provider admitted the anesthesia group that currently staffs the healthcare center I presented within will combine ropivacaine and Exparel® for use in peripheral nerve blocks. Since ropivacaine omits the dextrorotatory enantiomer of bupivacaine that lowers the threshold for cardiotoxicity, some anesthesia providers in the group felt it would be a safer option for patients (Kuthiala & Chaudhary, 2011). They believe it could help prevent the cardiotoxicity that can result from bupivacaine, and that it should still be safe to admix with Exparel® since ropivacaine is simply one enantiomer of bupivacaine (Kuthiala & Chaudhary, 2011). However, this would be considered an off-label use and is not yet recommended by Exparel®'s manufacturer (Pacira Pharmaceuticals, 2023). I thought I may see a bigger increase in the percentage of patients receiving Exparel® and ropivacaine in my post-session Epic data because of this conversation. The total percentage of patients receiving other local anesthetics in addition to Exparel® did increase slightly. The number of patients receiving ropivacaine and Exparel® increased from 0.8% (1/122 patients) to 3.9% (2/51 patients). It is possible there will be studies in the future that confirm the safety of admixing Exparel® as we continue to expand our knowledge on the use of pharmaceuticals.

It could also be useful to collect data on the incidence of LAST at this facility. Data could be collected from Epic, searching for patients with a diagnosis of LAST or a medication administration record including intralipids. While LAST is a rare event, it is also mostly preventable with provider knowledge and skill in administration of local anesthetics.

In the future, perhaps the electronic medical record algorithm for building alerts such as an intraoperative Epic alert will support creation of an Exparel® alert. Convenient notification of providers when a patient has received Exparel® could help anesthesia providers more easily

identify which patients should not receive additional local anesthetic. This alert would also have applications for enhanced recovery after surgery (ERAS) protocols, ensuring a patient has received numerous multimodal analgesics to promote early mobility, recovery, and discharge.

## Conclusion

Despite the success of the educational intervention increasing both the knowledge and awareness of the risks associated with Exparel® administration followed by the subsequent administration of additional local anesthetics, the incidence of this clinical event did not decrease. It is conceivable the creation and implementation of a provider alert in the electronic medical record, which was not possible at this writing, would reduce the frequency of additional local anesthetic administration following Exparel® administration.

In the future, I anticipate additional studies involving alternative uses or doses of Exparel® will be completed and the prescribing guidelines will be altered to reflect new knowledge. Throughout the course of this project, this has already proven true, as Pacira Pharmaceuticals added two new approved indications for Exparel® in 2023 as clinical trials were completed. Safety and efficacy of Exparel® was proven in clinical trials for both adductor canal blocks and sciatic nerve blocks in the popliteal fossa (Pacira Pharmaceuticals, 2023). Currently, there are numerous clinical trials involving the use of Exparel® I was able to identify within the United States, with more internationally. Anesthesia providers should be forever learners and continuously adapt their practice as new evidence-based practice information becomes available. Staying up to date on current safest practice may include attending educational presentations such as the one I presented, conferences, case study meetings, or continuing education units.

This project will be disseminated at a doctorate of nursing practice poster day on April 12th, 2024 via a brief presentation and poster summarizing the key points of this project. The hospital where this project took place will receive the results of this project via email to the chief registered nurse anesthetist and hospital institutional review board.

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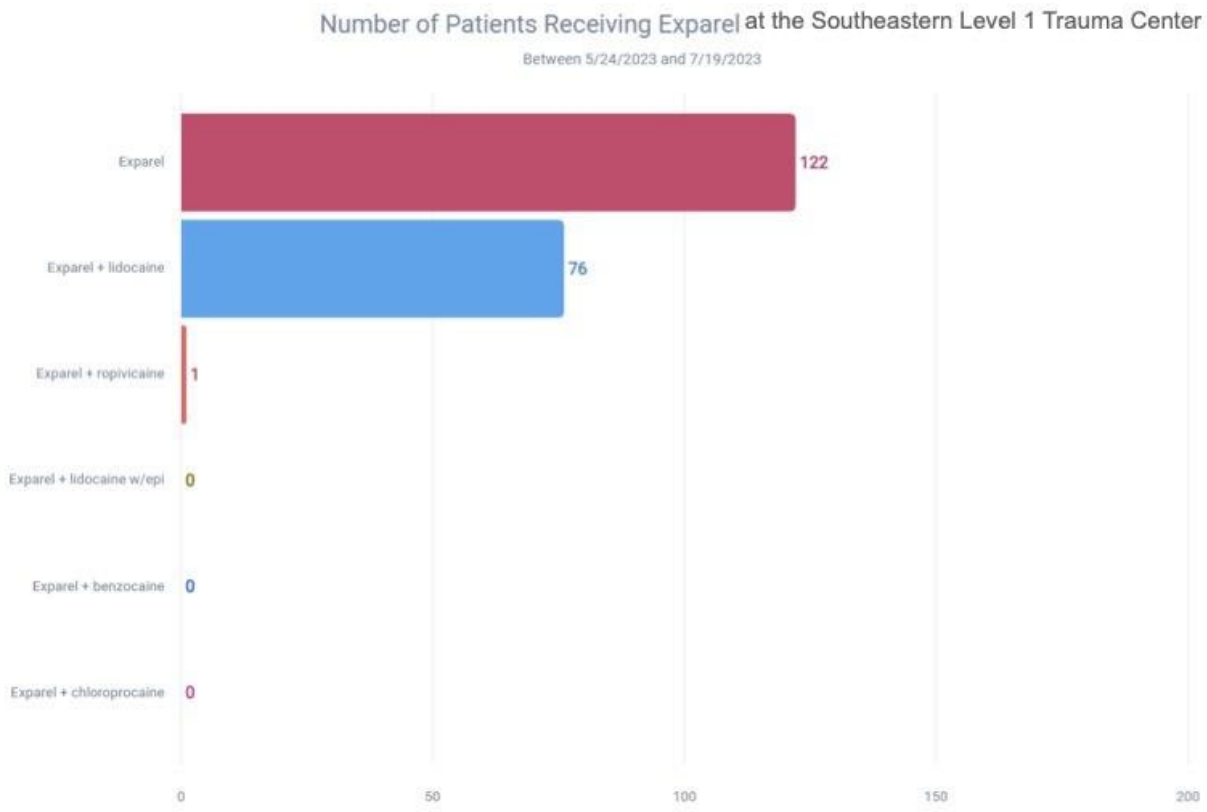
## Appendix A: Pre-Implementation Chart of the Number of Patients Receiving Exparel



## Appendix B: Test Distributed to Providers Before and After Educational Session

### Exparel® Pre-Test

Directions: Please circle 1 answer for each question. Do not write your name or any other identifying information on this quiz. Thank you!

1. The local anesthetic contained in Exparel® is:
   a. Lidocaine
   b. Bupivacaine
   c. Tetracaine
   d. Chloroprocaine

2. The maximum recommended dose of Exparel® for regional nerve blocks in adults is:
   a. 65 mg
   b. 133 mg
   c. 266 mg
   d. 399 mg

3. To limit the risk of local anesthetic systemic toxicity after administration of Exparel®, no additional local anesthetic should be administered for:
   a. 24 hours
   b. 48 hours
   c. 72 hours
   d. 96 hours

4. Documentation of a previous administration of Exparel® can currently be found:
   a. On the Exparel® patient bracelet
   b. In the MAR
   c. Exparel® administration paper in the chart
   d. All of the above

5. Treatment of local anesthetic toxicity should include:
   a. Beta blockers
   b. Calcium channel blockers
   c. Lipid emulsion
   d. Lidocaine boluses

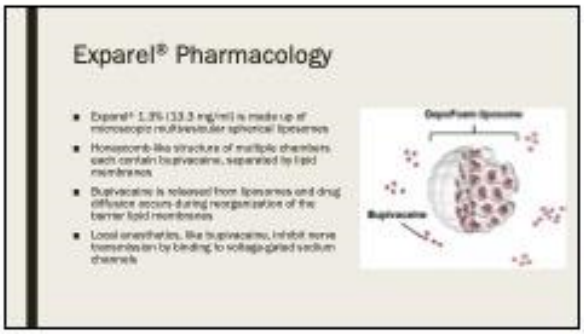
## Appendix C: Test Distributed to Providers with Correct Answers Shown in Red

Exparel® PreTest/PostTest

1. The local anesthetic contained in Exparel® is:
   a. Lidocaine
   b. Bupivacaine
   c. Tetracaine
   d. Chloroprocaine
2. The maximum recommended dose of Exparel® for regional nerve blocks in adults is:
   a. 65 mg
   b. 133 mg
   c. 266 mg
   d. 399 mg
3. To limit the risk of local anesthetic toxicity after administration of Exparel® no additional local anesthetic should be administered for:
   a. 24 hours
   b. 48 hours
   c. 72 hours
   d. 96 hours
4. Documentation of a previous administration of Exparel® can currently be found:
   a. On the Exparel® patient bracelet
   b. In the MAR
   c. Exparel® administration label in the chart
   d. All of these
5. Treatment of local anesthetic toxicity should include:
   a. Beta blockers
   b. Calcium channel blockers
   c. Lipid emulsion
   d. Lidocaine boluses

# Appendix D: Educational PowerPoint Presentation Slides


1

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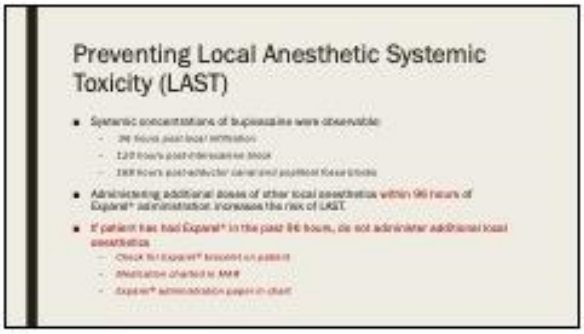
3

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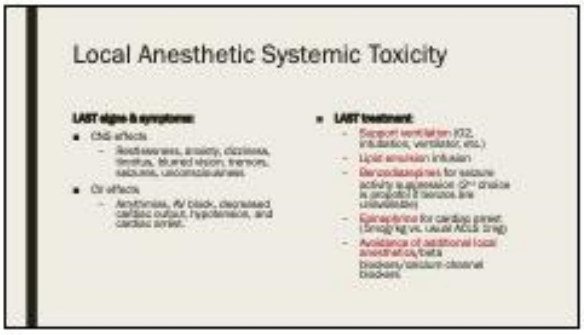
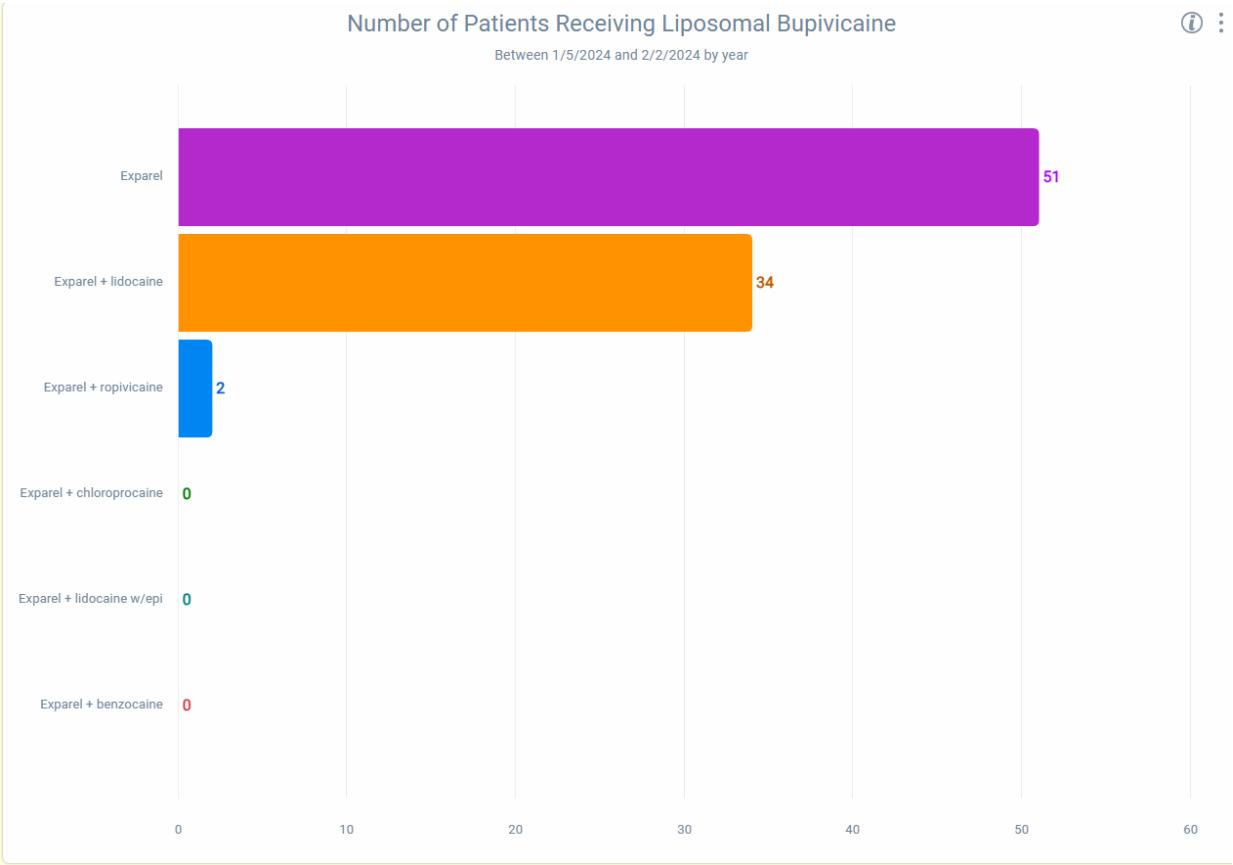



5


6

## Appendix E: Post-Implementation Chart of the Number of Patients Receiving Exparel



# Appendix F: Paired t-Test Two Sample for Means

t-Test: Paired Two Sample for Means

| | *Pretest score* | *Post-test score* |
|---|---|---|
| Mean | 3.72 | 4.36 |
| Variance | 0.376666667 | 0.323333333 |
| Observations | 25 | 25 |
| Pearson Correlation | 0.181479892 | |
| Hypothesized Mean Difference | 0 | |
| df | 24 | |
| t Stat | -4.22616435 | |
| P(T<=t) one-tail | 0.000148553 | |
| t Critical one-tail | 1.71088208 | |
| P(T<=t) two-tail | 0.000297105 | |
| t Critical two-tail | 2.063898562 | |