Pain Management After Appendectomy and Cholecystectomy: An Innovative Protocol Using Exparel

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To reduce post-operative pain correlates such as opioid consumption and length of stay, a novel pain management protocol has been utilized for laparoscopic appendectomy and laparoscopic cholecystectomy. Research was performed on a retrospective patient population who were given local anesthetic for pain management, specifically liposomal bupivacaine, also known as Exparel. The objective was to determine if using the most recent protocol utilizing Exparel had any effect on pain correlates such as opioid consumption or post-operative or total length of stay. Results showed that the use of the most recent Exparel protocol results in a statistically significant decrease in opioid consumption. Results also show that the pain management protocol used had no significant effect on post-operative or total length of stay.
PAIN MANAGEMENT AFTER APPENDECTOMY AND CHOLECYSTECTOMY: AN INNOVATIVE PROTOCOL USING EXPAREL

Pete Newman, B.S.

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PAIN MANAGEMENT AFTER APPENDECTOMY AND CHOLECYSTECTOMY: AN INNOVATIVE PROTOCOL USING EXPAREL

INTERNSHIP PRACTICUM REPORT

Presented to the Graduate Council of the Graduate School of Biomedical Sciences University of North Texas Health Science Center at Fort Worth
In Partial Fulfillment of the Requirements

For the Degree of

MASTERS OF SCIENCE IN CLINICAL RESEARCH MANAGEMENT

BY

Pete Newman, B.S.
Fort Worth, Texas
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I would like to thank Dr. Laura Petrey for allowing me the opportunity to intern at Baylor University Medical Center in the Department of Trauma Research, as well as offering guidance and instruction to help me design and execute my research. Furthermore, I appreciate her dedication to ensuring the quality of my work was up to par.

I want to thank my major professor, Dr. Jerry Simecka, for helping me understand the research process and what is to be expected, for taking the time to read through my research proposal and my thesis to offer critical feedback, and for easing my concerns about the process. I would also like to thank Dr. Stephen Mathew for helping me stay on track and reminding me of important details, as well as working with me to make sure that my project is feasible and realistic. Thank you to Dr. Dong-Ming Su for offering constructive feedback on my research proposal and my thesis.

Also a very special thank you to the other research staff in my department, Evan Rainey, Mackenzie Dome, and Mark Powers. Without their help reviewing my material, helping me learn correct procedure and all of the programs that we use, their hands-on assistance, and the answering of my incessant questions, I would not have been as successful as I am. And, very special thank you to Jordin Shelley and Lauren Baskett for volunteering their time to help me with data input and revising of my thesis, and to Jacob Roden-Foreman for helping me graph my data.
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CHAPTER I

INTRODUCTION

Since the days of ancient Sumeria, thousands of years BC, opiates have been used for pain management. Opiates were unregulated and legal for consumption in the United States as late as the 20th century. It wasn’t until 1924 that the sale and possession of the drug Heroin was made illegal. As technology and understanding of how the human body responds to opioids has advanced, so has the potency of these drugs. To put it in relative terms, a typical dose of intravenous morphine – the standard analgesic for pain – is 10 milligrams. For Dilaudid, a synthetic opioid also known as hydromorphone, a typical dose may be 1.5 milligrams for the same amount of pain relief. Fentanyl, another synthetic opioid, would have a typical dose of 200 micrograms, or 0.2 milligrams. For the more recent synthetic opioids the therapeutic window becomes much narrower, and thus the risk of severe side effects such as respiratory depression and death become significantly greater.

In an attempt to alleviate the problem, the U.S. Department of Health and Human Services and the National Institutes of Health have been working to improve access to addiction treatment, maintain accurate statistics on the current epidemic, investigating safe alternatives to manage chronic pain, and develop effective reversal interventions should someone overdose.

This study was conducted at Baylor University Medical Center (BUMC) in Dallas, Texas. At BUMC, there are over 900 beds in three separate hospitals, over 1,200 physicians, and over 37,000 annual admissions. BUMC is also the home of the Baylor Scott & White Research Institute which is currently overseeing over 2000 research projects across a multitude of specialties.
The principle investigator, Dr. Laura B. Petrey, is a specialist in acute care general surgery, trauma, and surgical critical care. She is an Assistant Professor of Surgery at the Texas A&M Health Science Center, and holds the distinction of being the first female General Surgery Attending at BUMC. She was previously the Associate Program Director for research in the Department of Surgery, and is currently the President of the Medical Staff at BUMC. Her primary areas of interest include hospital readmission, cost effectiveness, and post-traumatic stress disorder (PTSD) in trauma patients. Dr. Petrey incorporated a long-acting local anesthetic, Exparel (liposomal Marcaine), in an attempt to investigate alternatives to giving opioids for pain management. Starting in June of 2013, Dr. Petrey used Exparel in laparoscopic appendectomies and cholecystectomies with the goal of reducing postoperative pain.
CHAPTER II

PROBLEM & HYPOTHESIS

A major problem in the world of western medicine has cropped up relatively recently, and that problem is addiction to prescribed opioid pain medications; a problem which is only getting worse.\textsuperscript{14,15} Because of this fact, it is in the best interest of health care providers and the makers of policy to reverse this trend by implementing alternative methods. Opioid medications, ranging from Tylenol-3 Codeine to Fentanyl, are commonly given to patients for acute pain. For our purposes, we will examine opiate consumption after surgery as a correlate for postoperative pain. A reduction in postoperative pain will ultimately lead to a reduction in hospital length of stay, and a reduction in inpatient and outpatient opioid consumption.\textsuperscript{22,24} Consumption of opiates has been shown to have side effects such as nausea, vomiting, constipation, respiratory depression, and death.\textsuperscript{30,38}

Exparel is a non-opioid local anesthetic with high efficacy in reducing post-operative pain and reduction in opioid medication use.\textsuperscript{22,24} Exparel is different than a traditional local anesthetic due to the liposomal technology that it employs. The liposomes contains the local anesthetic bupivacaine, which is slowly released as the liposome is broken down.\textsuperscript{10} Although Exparel has a high level of efficacy in reducing postoperative pain, one of the major criticisms of it has been its cost.\textsuperscript{20,21,22} For example, a vial of bupivacaine HCl costs approximately $3, but a vial of Exparel would cost almost one hundred times that amount, with a hefty price tag of $285.\textsuperscript{17} In the operating room at Baylor University Medical Center, the price of a 20 mL vial of Exparel is $377. Although the cost of Exparel is significantly higher than the anesthetics used in the old protocol, its use can reduce total length of hospital stay.\textsuperscript{22,24} Thus, paying the extra cost of
Exparel may reduce opioid related side effects and overall health care cost through reduced length of stay.

The protocol that we are investigating is diluting a 20 mL vial of Exparel containing 266mg of liposomal bupivacaine with 20 mL of normal saline and 30 mL of 0.5% Marcaine. Marcaine with epinephrine provides excellent fast acting analgesic effect, but that effect only lasts approximately six to eight hours, which may increase the need for opiates in the long term.\textsuperscript{24,25} Undiluted Exparel has an excellent long term effect, but takes approximately 30 to 90 minutes to take effect – up to 6 hours for full effect – depending on the vascularity of the area, compared to the 10-15 minutes required of Bupivacaine HCl or 2-5 minutes for Lidocaine for example.\textsuperscript{17,29} Because of this fact, it is now suggested by Pacira to dilute the Exparel with Marcaine and normal saline to couple the fast acting and long term effects of both Marcaine and liposomal bupivacaine respectively. This new protocol of diluting the Exparel should be more effective at non-opioid pain management than the Marcaine with epinephrine or undiluted Exparel.

I hypothesize that the most recent protocol used by Dr. Petrey, which I have labeled “New Exparel,” will result in a reduction of pain correlates such as opioid medication use, postoperative length of stay in the hospital, as well as conferring reduced total hospital cost to the patient.

**Hypothesis:** The use of diluted Exparel will result in a reduction of pain correlates compared to old pain management protocol.

**Aim 1:** Show that diluted Exparel provides a reduction of overall pain in laparoscopic appendectomy compared to old pain management protocol
**Aim 2:** Show that diluted Exparel provides a reduction of overall pain in laparoscopic cholecystectomy compared to old pain management protocol

**Aim 3:** Show that diluted Exparel provides a reduction of overall pain in laparoscopic cholecystectomy with intraoperative cholangiogram compared to old pain management protocol
CHAPTER III

BACKGROUND

Historically, the procedure to remove the appendix and gallbladder – appendectomy and cholecystectomy, respectively – was done as an open procedure. More recently however, surgeons have adopted the laparoscopic approach as the method of choice. First described in 1980 by a German gynecologist, Dr. Kurt Semm, the laparoscopic approach to appendectomy has since become the standard method.\textsuperscript{18} Approximately five years later, the method for performing a laparoscopic cholecystectomy was described by Dr. Med Erich Mühe in 1985.\textsuperscript{19} In comparison to traditional open surgeries, laparoscopic procedures typically reduce postoperative pain, thus reducing the need for opioid pain medication, and reduce total time in the hospital.\textsuperscript{1} If the attending physician is concerned about a gallstone stuck in the common bile duct – also known as choledocholithiasis – or the patient having an congenital abnormality of the biliary system, a cyst or fistula, they may elect to perform an intraoperative cholangiogram (IOC).\textsuperscript{31} To perform an IOC, a clip is placed on the cystic duct to prevent flow of contrast material into the gallbladder, and then the biliary is filled with contrast dye and X-Ray imaging is performed.\textsuperscript{32,33} If a stone is identified in the common bile duct, the attending physician will attempt to flush the stone out of the bile duct, but if that is unsuccessful then the attending will consult with a Gastrointestinal (GI) specialist about performing an Endoscopic Retrograde Cholangiopancreatography (ERCP).\textsuperscript{33,34} This procedure serves to clear the blockage of the bile duct and allow bile to flow normally.\textsuperscript{34} Some surgeons may perform laparoscopic or common bile duct explorations to remove the stone, but Dr. Petrey typically does not do this.
Although using laparoscopy has reduced overall pain and length of stay compared to open surgery, there remains a significant pain profile as it is still a surgical procedure.² Laparoscopic surgeries are normally performed with a local anesthetic in addition to general anesthesia, with typical choices being lidocaine or Marcaine with or without epinephrine. However, a downside to these local anesthetics is that they are relatively short acting and still result in significant postoperative pain.³

The protocol that Dr. Petrey is currently utilizing in her laparoscopic appendectomies involves using the diluted Exparel formulation to anesthetize the periportal areas around the umbilicus, the left lower quadrant (LLQ) of the abdomen to anesthetize the ilioinguinal and genitofemoral nerves, and the suprapubic area. To achieve this, Exparel solution is injected around the first port site in the subcutaneous tissues, then the first port is placed left of the umbilicus for the first trocar and laparoscope. For the remaining ports, the subcutaneous tissues are anesthetized, followed by anesthesia of the retro rectus space to target the spinal nerves. The Exparel solution is dispersed in a “ray-like” fashion to distribute the liposomes equally. After this, the remaining ports are placed in the suprapubic area and LLQ for the remaining trocars, then remaining solution is injected in the retro rectus space around the first port. This procedure is diagrammed in Figure 1. The yellow represents areas that are anesthetized, and the black lines represent incision sites.

*Figure 1: Laparoscopic Appendectomy*
For laparoscopic cholecystectomies, the same diluted Exparel mixture is used to anesthetize along the area just inferior to the right anterior ribs, around the umbilicus, and along the right anterior abdominal wall to anesthetize the genitofemoral and ilioinguinal nerves. Three ports are placed inferior to the ribs: one inferior to the xiphoid process, one slightly lower on the midclavicular line, and one anterior to the midaxillary line. Another port is placed superiorly and to the right of the umbilicus. First, the diluted Exparel is injected around the first port site and the first port is placed. Then the Exparel solution is injected along the costal margin in the retro rectus space. This is followed by the injection of Exparel is injected along the right lateral abdominal wall as well as using the TAP block technique to anesthetize the spinal nerves supplying the abdomen. For the remaining ports, the subcutaneous tissues and the retro rectus space around the port sites are anesthetized. The Exparel is dispersed in a “ray-like” fashion to distribute the liposomes equally. When this is completed, the remaining ports are placed, and the remaining Exparel solution is injected around the first port site. This procedure is diagrammed in Figure 2. The yellow represents areas that are anesthetized, and the black lines represent incision sites.

Figure 2: Laparoscopic Cholecystectomy
One of the methods that anesthesiologists have been using to reduce postoperative pain is known as a transversus abdominis plane block, or TAP block. First described in 2001, the TAP block is a procedure involving the use of external landmarks on the body to locate the Triangle of Petit. The landmarks of the Triangle of Petit are shown below in figure 3.

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Figure 3: Triangle of Petit

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The Triangle of Petit is bordered anteriorly by the external oblique muscle, posteriorly by the latissimus dorsi, and inferiorly by the iliac crest. The goal of this technique is to anesthetize the anterior rami of the T6-L1 nerves, which run between the internal oblique and transversus abdominis muscles. Once the triangle is located, a long needle is inserted and localized by using what is known as the “two pop” technique. The first “pop” is felt when the needle pierces the fascia of the external oblique muscle, followed by a second “pop” where the needle pierces the fascia of the internal oblique muscle. If performed correctly, this localizes the needle between the internal oblique muscle and the transversus abdominis where the local anesthetic is to be injected. Physicians often use an ultrasound probe to help them guide the needle into the correct region. Use of ultrasound has significantly decreased the number of adverse events in
comparison to the landmark technique.\textsuperscript{7} If a TAP is performed correctly, this will anesthetize the anterior abdominal skin, muscles, and parietal peritoneum.\textsuperscript{5}

The basic function of a local anesthetic is to provide analgesia to a targeted area of tissue. This is achieved by the blocking of conduction in peripheral nerves through reversible inhibition of sodium channels. With the sodium channel blocked, the nerve cannot depolarize thus rendering it unable to transmit action potentials. Interesting to note, however, that the blocking of nerves seems to inhibit sensory nerves while sparing motor nerves.\textsuperscript{8} There are two classes of local anesthetics: amino amide type and aminoester type. Both types of anesthetics achieve the same overall effect, but there are some differences in their pharmacokinetics. Amide type anesthetics are metabolized in the liver, while ester type anesthetics are metabolized by pseudocholinesterases in the plasma. This means that ester types are less stable in solution compared to amide types, which reduces the effect duration. Furthermore, the ester type has been shown to be more likely to cause allergic reaction when compared to amide type.\textsuperscript{7,8} Common amide type anesthetics include lidocaine, bupivacaine, and ropivacaine. Common ester type anesthetics include tetracaine and benzocaine.\textsuperscript{8} As mentioned previously, one of the downsides of a local anesthetic is the relatively short duration of action. Advances in technology have allowed development of methods to significantly increase the duration of analgesia, in this case through the use of a liposomal delivery system. In short, the anesthetic is stored within cavities in a liposome, and is slowly released as the body breaks down the walls of the liposome, giving longer lasting nerve blocking effect.\textsuperscript{9} The company Pacira Pharmaceuticals has applied this principle to create liposomal bupivacaine, otherwise known by its brand name Exparel.

Exparel utilizes a liposomal delivery system which is known as DepoFoam. The bupivacaine is stored within the chambers until the body either dissolves the walls of the
chamber or molecular reconfiguration allows for release of the bupivacaine. In either case, the analgesic effect of the bupivacaine is significantly increased in duration from approximately 6-8 hours found with non-liposomal bupivacaine to approximately 72 hours. Since Exparel utilizes liposomal technology, it can be noted that there is a delayed initial effect as the body takes time to break down the liposome. Therefore, it is suggested by Pacira Pharmaceuticals that the Exparel be mixed with non-liposomal bupivacaine to allow for the immediate effect, while the liposomal bupivacaine is released over time giving the long-term effect. Since the toxic effect of the liposomal and non-liposomal bupivacaine is additive, it is suggested to use this with caution. Exparel has been shown to have excellent effect in terms of postoperative pain reduction, with surgeries such as arthroplasty, hernia repair, and breast augmentation. This reduction in overall pain ultimately leads to reduction in usage of opioid pain medication, and total length of stay.

SIGNIFICANCE

Drug addiction, or more specifically opiate addiction, is a public health crisis in the United States, with an estimated 2.1 million people in the US alone that suffer from disorders related to prescription pain medication. It is estimated that as many as 1 in 5 patients with a pain related diagnosis receive opioids to manage their pain. In 2012, as many as 1 in 15 patients prescribed opioids ended up chronic users or as abusers. So far in 2017, the rate of opioid overdose mortality for synthetic and non-synthetic opioids exceeded the rate of overdose for Heroin and Cocaine combined.

The cost of healthcare in the United States has increased significantly over the past 20 years. In 2015, the per capita expenditure on health care alone was $9,990, or approximately $3.2
trillion on a national level. Almost a third, or 32.3% of that is on hospital care, with 10.2% being on prescription medications.\textsuperscript{13}

Currently, Exparel is already being used to great effect in reducing opioid consumption postoperatively in other common surgeries, so implementing its use in laparoscopic appendectomies and cholecystectomies would be a safe expansion of protocol.\textsuperscript{20,21,22} If the implementation of the new protocol works in the way hypothesized, there is great potential to see a significant reduction in opiate usage across the United States.

This protocol will, by extension, reduce the burden on healthcare systems, reduce the incidence of opiate related side effects, and reduce the rate of opiate addiction.
CHAPTER IV

METHODS

This research report is a retrospective study reaching from January 1, 2012 to August 31, 2017. The patients are initially separated into three groups: patients who underwent a laparoscopic appendectomy, patients who underwent a laparoscopic cholecystectomy, and patients who underwent a laparoscopic cholecystectomy with intraoperative cholangiogram (IOC). From these three groups, the patients are separated into three cohorts: patients that received a local anesthetic injection of Marcaine with or without epinephrine, patients that received undiluted Exparel, and patients that received diluted Exparel. The third cohort, or diluted Exparel cohort, is divided into two subgroups: patients who received Exparel diluted with greater than 20 mL of normal saline and patients who received Exparel diluted with 20 mL of normal saline. The third cohort will be compared to the first two cohorts using them as a control. The temporal relationship of the cohorts is described in figure 4.

Figure 4: Timeline

2012 - 2013 | 2013 - 2014 | 2015 - 2016 | 2015 - Present  
Pre-Exparel | Undiluted Exparel | Old Exparel | New Exparel
The data is split into eight groups. Of the patients who underwent a laparoscopic appendectomy, the first group are those who received only Marcaine with or without epinephrine and no Exparel. The second group received undiluted Exparel, which is only Exparel and neither Marcaine nor normal saline. The third group received Exparel diluted with greater than 20 mL normal saline. The fourth group received Exparel diluted with 30 mL 0.5% Marcaine with epinephrine and 20 mL normal saline. Of the patients who underwent laparoscopic cholecystectomy, the first group are those who received Marcaine with epinephrine which will be referred to as “Pre-Exparel,” the second group received undiluted Exparel which will be referred to as “Undiluted Exparel,” the third group received Exparel diluted with greater than 20 mL normal saline which will be referred to as “Old Exparel,” and the fourth group received Exparel diluted with 20 mL normal saline which will be referred to as “New Exparel.” Of the patients who underwent laparoscopic cholecystectomy with IOC, the first group are those who received Marcaine with epinephrine, the second group received undiluted Exparel, the third group received Exparel diluted with greater than 20 mL normal saline, and the fourth group received Exparel diluted with 20 mL normal saline. Some of the patients did not fall perfectly into these specific date ranges, so this is more of a general description. The appendectomy and cholecystectomy groups will be compared separately. This relationship and the number of patients in each group is diagrammed in figure 5.

*Figure 5: Sampling groups*

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Laparoscopic Appendectomy</strong></td>
<td>n = 41</td>
<td>n = 40</td>
<td>n = 19</td>
<td>n = 24</td>
</tr>
<tr>
<td><strong>Laparoscopic Cholecystectomy</strong></td>
<td>n = 41</td>
<td>n = 52</td>
<td>n = 26</td>
<td>n = 23</td>
</tr>
<tr>
<td><strong>Laparoscopic Cholecystectomy w/ IOC</strong></td>
<td>n = 60</td>
<td>n = 49</td>
<td>n = 18</td>
<td>n = 27</td>
</tr>
</tbody>
</table>
The specific variables that will be compared are opioid medication use (measured in morphine milligram equivalents), length of stay in hospital (measured in hours), and total cost of hospital visit (measured in dollars).

Inclusion Criteria:

- First admitted to Baylor University Medical Center from January 1, 2005 through present
- Underwent laparoscopic cholecystectomy or appendectomy performed or supervised by Dr. Petrey

Exclusion Criteria:

- Aged < 18 years
- Chronic Pain Syndrome
- Taking opioid medication(s) on admission
- History of allergic hypersensitivity to amide-type local anesthetics
- Pregnancy
- Severe chronic kidney disease
- Admission into the Intensive Care Unit (ICU)

Opioid consumption will be divided between types of opioid medication (e.g. morphine, dilaudid, etc.), whether they were given intravenously (IV) or by mouth (PO), and whether the dose is given while in the operating room (OR), on a set schedule (Scheduled), or as needed by the patient (PRN).

Demographic and clinical characteristics were summarized using means and standard deviations or counts and percentages. The primary outcome variables (total opioid dose and length of stay) were summarized using means and standard deviations, medians and inter-
quartile ranges, and ranges due to them being skewed. All binary variables were compared across groups using chi-square or Fisher’s exact tests if the counts were small. Age was compared using analysis of variance (ANOVA) and the primary outcome variables were compared using the non-parametric Kruskal-Wallis test since they did not meet the normal distribution assumption. Primary outcomes that were significant across groups were then analyzed using separate Mann-Whitney tests for pairwise comparisons to determine which groups were statistically significant. The p-values were adjusted using the Holm-Bonferroni technique. All analysis was performed using SAS 9.4 with a 5% significance level.
CHAPTER V

RESULTS & DISCUSSION

Laparoscopic Cholecystectomy

There were 139 total patients who received a laparoscopic cholecystectomy between January 1, 2012 and August 31, 2017. Of these 139 patients, 7 were admitted to the ICU, 5 patients were pregnant at the time of admission, 1 patient had incomplete records, and 2 patients expired. Out of the remaining 124 patients, 30 patients were male and 94 were female. The average age of the Pre-Exparel group is 41.8 ± 18.2 years, of the Undiluted Exparel group is 38.8 ± 14.4 years, of the Old Exparel group is 44.7 ± 13.4 years, and of the New Exparel group is 46.5 ± 19.4 years. There were 5 patients who presented with perforation of the gallbladder, 86 patients who presented with symptomatic cholelithiasis, 8 patients who presented with gangrenous gallbladder, 0 patients who presented with pericholecystic abscess, 15 patients who presented with choledocholithiasis, and 27 patients who presented with hydrops of the gallbladder. Other operative findings include 2 patients with umbilical hernia, 4 patients with cholecystostomy tubes, 1 with appendicolith, and 1 with ovarian mass. There were 4 patients with post-operative complications, including 1 patient with wound infection, 2 patients with retained choledocholithiasis, and 1 patient with bile leak. There were 9 patients total that received the ERCP procedure. This information is summarized in on the next page in Table 1.
Table 1: Summary of demographic, operative findings, and post-op complications and considerations

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Pre-Exparel (n=41)</th>
<th>Undiluted Exparel (n=40)</th>
<th>Old Exparel (n=19)</th>
<th>New Exparel (n=24)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at Procedure</td>
<td>41.8±18.2</td>
<td>38.8±14.4</td>
<td>44.7±13.4</td>
<td>46.5±19.4</td>
<td>0.3036</td>
</tr>
<tr>
<td>Male Gender</td>
<td>5 (12.2%)</td>
<td>10 (25%)</td>
<td>5 (26.3%)</td>
<td>10 (41.7%)</td>
<td>0.0636</td>
</tr>
</tbody>
</table>

### Operative Findings

<table>
<thead>
<tr>
<th>Findings</th>
<th>Pre-Exparel (n=41)</th>
<th>Undiluted Exparel (n=40)</th>
<th>Old Exparel (n=19)</th>
<th>New Exparel (n=24)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perforation</td>
<td>2 (4.9%)</td>
<td>3 (7.5%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0.5035</td>
</tr>
<tr>
<td>Symptomatic Cholelithiasis</td>
<td>25 (61%)</td>
<td>32 (80%)</td>
<td>13 (68.4%)</td>
<td>16 (66.7%)</td>
<td>0.3110</td>
</tr>
<tr>
<td>Gangrene</td>
<td>2 (4.9%)</td>
<td>2 (5%)</td>
<td>1 (5.3%)</td>
<td>3 (12.5%)</td>
<td>0.6994</td>
</tr>
<tr>
<td>Pericholecystic Abscess</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>NA</td>
</tr>
<tr>
<td>Choledocholithiasis</td>
<td>4 (9.8%)</td>
<td>5 (12.5%)</td>
<td>2 (10.5%)</td>
<td>4 (16.7%)</td>
<td>0.8440</td>
</tr>
<tr>
<td>Hydrops of the Gallbladder</td>
<td>13 (31.7%)</td>
<td>10 (25%)</td>
<td>3 (15.8%)</td>
<td>1 (4.2%)</td>
<td><strong>0.0474</strong></td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Umbilical Hernia</td>
<td>1 (2.4%)</td>
<td>1 (2.5%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>NA</td>
</tr>
<tr>
<td>Cholecystotomy tube</td>
<td>2 (4.9%)</td>
<td>2 (4.9%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>NA</td>
</tr>
<tr>
<td>Appendicolith</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (5.3%)</td>
<td>0 (0%)</td>
<td>NA</td>
</tr>
<tr>
<td>Ovarian mass</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (5.3%)</td>
<td>0 (0%)</td>
<td>NA</td>
</tr>
</tbody>
</table>

### Post-Op Complications/Considerations

<table>
<thead>
<tr>
<th>Complications</th>
<th>Pre-Exparel (n=41)</th>
<th>Undiluted Exparel (n=40)</th>
<th>Old Exparel (n=19)</th>
<th>New Exparel (n=24)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wound Infection</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (4.2%)</td>
<td>NA</td>
</tr>
<tr>
<td>Abscess</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>NA</td>
</tr>
<tr>
<td>Ileus</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>NA</td>
</tr>
<tr>
<td>Peritonitis</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>NA</td>
</tr>
<tr>
<td>Bowel Obstruction</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>NA</td>
</tr>
<tr>
<td>Bile Leak</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>NA</td>
</tr>
<tr>
<td>Retained Choledocholithiasis</td>
<td>1 (2.4%)</td>
<td>1 (2.5%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>NA</td>
</tr>
<tr>
<td>Incisional Hernia</td>
<td>1 (2.4%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>NA</td>
</tr>
<tr>
<td>Endoscopic Retrograde Cholangio-Pancreatography</td>
<td>3 (7.3%)</td>
<td>1 (2.5%)</td>
<td>2 (10.5%)</td>
<td>3 (12.5%)</td>
<td>0.3545</td>
</tr>
</tbody>
</table>

*Post-hoc pairwise comparisons showed significant differences between the Pre-Exparel and Undiluted Exparel groups versus the Old Exparel and New Exparel groups*
When examining the inpatient opioid consumption based on the anesthetic protocol, the data shows a statistically significant difference in the number of patients using hydrocodone PRN between the Pre-Exparel ($n = 30$), Undiluted Exparel ($n = 32$) and the Old Exparel ($n = 8$) and New Exparel ($n = 8$) protocols with a p-value of 0.0002. There is a statistically significant difference in the number of patients receiving scheduled (p = 0.0224) and PRN Tramadol (p = 0.0045), and Tylenol-3 tablets (p < 0.0001), however the total number people receiving these medications is so small that it is likely caused by a factor other than pain, thus is not likely to be clinically significant. There is not a statistically significant difference in number of patients given Dilaudid in the OR (p = 0.1535) and PRN (p = 0.7874) between groups, in number of patients given IV Morphine PRN (p = 0.3533) between groups, in number of patients given Fentanyl in the OR (p = 0.7417) and PRN (p = 0.3397) between groups, and in number of patients given Meperidine PRN (p = 1.0) between groups. There were no instances of patients receiving IV morphine in the OR, PO morphine, scheduled doses of Meperidine, either scheduled or PRN doses of Oxycodone or Percocet, or scheduled doses of Tylenol-3 Codeine. These data are summarized on the next page in Table 2.
Table 2: Opioid Medication usage and total dose

<table>
<thead>
<tr>
<th>Opioid Medications</th>
<th>Pre-Exparel</th>
<th>Undiluted Exparel</th>
<th>Old Exparel</th>
<th>New Exparel</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocodone</td>
<td>30 (73.2%)</td>
<td>32 (80%)</td>
<td>8 (42.1%)</td>
<td>8 (33.3%)</td>
<td>0.0002*</td>
</tr>
<tr>
<td>Dilaudid OR</td>
<td>17 (41.5%)</td>
<td>19 (47.5%)</td>
<td>12 (63.2%)</td>
<td>7 (29.2%)</td>
<td>0.1535</td>
</tr>
<tr>
<td>Dilaudid PRN</td>
<td>18 (43.9%)</td>
<td>18 (45%)</td>
<td>6 (31.6%)</td>
<td>10 (41.7%)</td>
<td>0.7874</td>
</tr>
<tr>
<td>IV Morphine OR</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>N/A</td>
</tr>
<tr>
<td>IV Morphine PRN</td>
<td>20 (48.8%)</td>
<td>20 (50%)</td>
<td>6 (31.6%)</td>
<td>8 (33.3%)</td>
<td>0.3533</td>
</tr>
<tr>
<td>PO Morphine OR</td>
<td>40 (97.6%)</td>
<td>39 (97.5%)</td>
<td>18 (94.7%)</td>
<td>24 (100%)</td>
<td>0.7417</td>
</tr>
<tr>
<td>PO Morphine PRN</td>
<td>11 (26.8%)</td>
<td>18 (45%)</td>
<td>7 (36.8%)</td>
<td>7 (29.2%)</td>
<td>0.3397</td>
</tr>
<tr>
<td>Meperdine Scheduled</td>
<td>(0%)</td>
<td>(0%)</td>
<td>(0%)</td>
<td>(0%)</td>
<td>N/A</td>
</tr>
<tr>
<td>Meperdine PRN</td>
<td>1 (2.4%)</td>
<td>1 (2.5%)</td>
<td>0 (0%)</td>
<td>1 (4.2%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Tramadol Scheduled</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>2 (10.5%)</td>
<td>0 (0%)</td>
<td>0.0224</td>
</tr>
<tr>
<td>Tramadol PRN</td>
<td>5 (12.2%)</td>
<td>1 (2.5%)</td>
<td>0 (0%)</td>
<td>4 (16.7%)</td>
<td>0.0045</td>
</tr>
<tr>
<td>Oxycodone Scheduled</td>
<td>(0%)</td>
<td>(0%)</td>
<td>(0%)</td>
<td>(0%)</td>
<td>N/A</td>
</tr>
<tr>
<td>Oxycodone PRN</td>
<td>(0%)</td>
<td>(0%)</td>
<td>(0%)</td>
<td>(0%)</td>
<td>NA</td>
</tr>
<tr>
<td>Percocet Scheduled</td>
<td>(0%)</td>
<td>(0%)</td>
<td>(0%)</td>
<td>(0%)</td>
<td>N/A</td>
</tr>
<tr>
<td>Percocet PRN</td>
<td>(0%)</td>
<td>(0%)</td>
<td>(0%)</td>
<td>(0%)</td>
<td>N/A</td>
</tr>
<tr>
<td>Tylenol Tablets Scheduled</td>
<td>(0%)</td>
<td>(0%)</td>
<td>(0%)</td>
<td>(0%)</td>
<td>N/A</td>
</tr>
<tr>
<td>Tylenol Tablets PRN</td>
<td>0 (0%)</td>
<td>1 (2.5%)</td>
<td>4 (21.1%)</td>
<td>7 (29.2%)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Post-hoc pairwise comparisons showed significant differences between the Pre-Exparel and Undiluted Exparel groups versus the Old Exparel and New Exparel groups.
When all opioid consumption is converted into morphine milligram equivalents (MME), the data show a statistically significant difference between the mean opioid consumption of the Pre-Exparel group (63.5 ± 32.2 MME) and the Undiluted Exparel group (74.2±73.4 MME) with the New Exparel group (47.4 ± 44.5 MME) with a p-value of 0.0047. It did not show a statistically significant difference between the Old Exparel group (53.9 ± 39.5 MME) and New Exparel group (47.4 ± 44.5 MME). Therefore, the data show that the use of the New Exparel protocol results in a 25% reduction of mean opioid consumption when compared to Pre-Exparel and a 36% reduction of mean opioid consumption when compared to Undiluted Exparel. The data also show an almost 50% reduction in median post-operative opioid consumption following a laparoscopic cholecystectomy when compared to Undiluted Exparel and Pre-Exparel protocol.

When comparing post-operative length of stay (LOS) in hours and minutes (hh:mm), the data show that the mean difference between LOS for Pre-Exparel (30:20 ± 19:31), Undiluted Exparel (29:08 ± 23:44), Old Exparel (32:23 ± 22:35) and New Exparel (37:12 ± 41:17) is not statistically significant. When comparing Total LOS, the data show that the mean difference between LOS for Pre-Exparel (45:57 ± 35:33), Undiluted Exparel (46:11 ± 30:23), Old Exparel (50:09±31:18) and New Exparel (58:45 ± 55:00) is not statistically significant. Therefore, it is reasonable to conclude that the New Exparel protocol does not cause a decrease in LOS. This data is summarized on the next page in Table 3 and graphically in figures 6-8.
<table>
<thead>
<tr>
<th></th>
<th>Pre-Exparel</th>
<th>Undiluted Exparel</th>
<th>Old Exparel</th>
<th>New Exparel</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Morphine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.0047*</td>
</tr>
<tr>
<td><strong>Equivalence Dose</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(mg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± Stdev</td>
<td>63.5 ± 32.2</td>
<td>74.2 ± 73.4</td>
<td>53.9 ± 39.5</td>
<td>47.4 ± 44.5</td>
<td></td>
</tr>
<tr>
<td>Median (Q1-Q3)</td>
<td>62 (40.6-77.5)</td>
<td>54.9 (37.1-84.5)</td>
<td>40.8 (32-57.5)</td>
<td>31.5 (24.5-48.5)</td>
<td></td>
</tr>
<tr>
<td>Min-Max</td>
<td>16.2 – 174.7</td>
<td>0 – 444.2</td>
<td>15.8-166</td>
<td>10-175.6</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.8363</td>
</tr>
<tr>
<td><strong>Post-Op Length</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>of Stay</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.8303</td>
</tr>
<tr>
<td><strong>Total Length of</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Stay</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± Stdev</td>
<td>45:57 ± 35:33</td>
<td>46:11 ± 30:23</td>
<td>50:09 ± 31:18</td>
<td>58:45 ± 55:00</td>
<td></td>
</tr>
</tbody>
</table>

*Post-hoc pairwise comparisons showed significant differences between Pre-Exparel and Undiluted Exparel groups versus the New Exparel group
Laparoscopic Cholecystectomy

**Figure 6**

Median total opioid consumption in morphine milligram equivalents in patients who underwent laparoscopic cholecystectomy. Box = 25th and 75th percentile; Bars = min and max values. N = 124 patients; n = 41 in Pre-Exparel, n = 40 in Undiluted Exparel, n = 19 in Old Exparel, n = 24 for New Exparel. Results show significant difference between Pre-Exparel and Undiluted Exparel groups versus the Old Exparel and New Exparel groups. Plots with star showed significant decrease. Outliers trimmed to show detail.

**Figure 7**

Median post-operative length of stay in hours in patients who underwent laparoscopic cholecystectomy. Box = 25th and 75th percentile; Bars = min and max values. N = 124 patients; n = 41 in Pre-Exparel, n = 40 in Undiluted Exparel, n = 19 in Old Exparel, n = 24 for New Exparel. Results show no significant difference in median post-operative length of stay across all groups. Outliers trimmed to show detail.
Fig 8. Median total length of stay in hours in patients who underwent laparoscopic cholecystectomy. Box = 25th and 75th percentile; Bars = min and max values. N = 124 patients; n = 41 in Pre-Exparel, n = 40 in Undiluted Exparel, n = 19 in Old Exparel, n = 24 for New Exparel. Results show no significant difference in median total length of stay across all groups. Outliers trimmed to show detail.
Laparoscopic Cholecystectomy with IOC

There was a total of 156 patients who underwent a Laparoscopic Cholecystectomy with intraoperative cholangiogram (IOC). Of these 156 patients, 8 patients were admitted to the ICU, 4 patients were pregnant at the time of admission, 1 patient was under age 18, and 1 patient had incomplete records. Out of the remaining 142 patients, 42 patients were male and 100 were female. The average age of the Pre-Exparel group is 44.6 ± 16.6 years, of the Undiluted Exparel group is 37.7 ± 14.3 years, of the Old Exparel group is 48.4 ± 19.6 years, and of the New Exparel group is 51.2 ± 16.3 years. There seems to be a statistically significant difference in age between groups (p = 0.0039). There was 1 patient with perforation of the gallbladder, 94 patients had symptomatic cholelithiasis, 12 patients with gangrenous gallbladder, 2 patients with pericholecystic abscess, 57 patients with choledocholithiasis, 17 patients with hydrops of the gallbladder. Other operative findings include 1 patient with umbilical hernia, 2 patients with cholecystostomy tube, and 1 patient with biliary pancreatitis. There were 4 patients with post-operative complications, including 1 patient with bowel obstruction, 1 patient with retained choledocholithiasis, and 2 patients with incisional hernia. There were 37 patients who underwent the ERCP procedure. These data are summarized on the next page in Table 4.
Table 4: Summary of demographic, operative findings, and post-op complications and considerations

<table>
<thead>
<tr>
<th></th>
<th>Pre-Exparel (n=41)</th>
<th>Undiluted Exparel (n=52)</th>
<th>Old Exparel (n=26)</th>
<th>New Exparel (n=23)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at Procedure</td>
<td>44.6 ± 16.6</td>
<td>37.7 ± 14.3</td>
<td>48.4 ± 19.6</td>
<td>51.2 ± 16.3</td>
<td><strong>0.0039</strong></td>
</tr>
<tr>
<td>Male Gender</td>
<td>11 (26.8%)</td>
<td>15 (28.8%)</td>
<td>7 (26.9%)</td>
<td>9 (39.1%)</td>
<td>0.7392</td>
</tr>
<tr>
<td><strong>Operative Findings</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perforation</td>
<td>1 (2.4%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0.6338</td>
</tr>
<tr>
<td>Symptomatic Cholelithiasis</td>
<td>33 (80.5%)</td>
<td>38 (73.1%)</td>
<td>10 (38.5%)</td>
<td>13 (56.5%)</td>
<td><strong>0.0021</strong></td>
</tr>
<tr>
<td>Gangrene</td>
<td>4 (9.8%)</td>
<td>1 (1.9%)</td>
<td>4 (15.4%)</td>
<td>3 (13%)</td>
<td>0.0816</td>
</tr>
<tr>
<td>Pericholecystic Abscess</td>
<td>1 (2.4%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (4.3%)</td>
<td>0.2936</td>
</tr>
<tr>
<td>Choledocholithiasis</td>
<td>18 (43.9%)</td>
<td>22 (42.3%)</td>
<td>9 (34.6%)</td>
<td>8 (34.8%)</td>
<td>0.8138</td>
</tr>
<tr>
<td>Hydrops of the Gallbladder</td>
<td>9 (22%)</td>
<td>5 (9.6%)</td>
<td>1 (3.8%)</td>
<td>2 (8.7%)</td>
<td>0.1519</td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Umbilical Hernia</td>
<td>0 (0%)</td>
<td>1 (1.9%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Cholecystotomy tube</td>
<td>2 (4.9%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Biliary pancreatitis</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (4.3%)</td>
<td></td>
</tr>
<tr>
<td><strong>Post-Op Complications/Considerations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wound Infection</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>N/A</td>
</tr>
<tr>
<td>Abscess</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>N/A</td>
</tr>
<tr>
<td>Ileus</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>N/A</td>
</tr>
<tr>
<td>Peritonitis</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>N/A</td>
</tr>
<tr>
<td>Bowel Obstruction</td>
<td>1 (2.4%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0.6338</td>
</tr>
<tr>
<td>Bile Leak</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>N/A</td>
</tr>
<tr>
<td>Retained Choledocholithiasis</td>
<td>0 (0%)</td>
<td>1 (1.9%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Incisional Hernia</td>
<td>0 (0%)</td>
<td>1 (1.9%)</td>
<td>0 (0%)</td>
<td>1 (4.3%)</td>
<td>0.5195</td>
</tr>
<tr>
<td>Endoscopic Retrograde Cholangio-Pancreatography</td>
<td>13 (31.7%)</td>
<td>11 (21.2%)</td>
<td>4 (15.4%)</td>
<td>9 (39.1%)</td>
<td>0.1788</td>
</tr>
</tbody>
</table>

*Age differences were found between the Undiluted group vs. both Old and New Exparel groups

**Post-hoc pairwise comparisons showed significant differences between the Pre-Exparel and Undiluted Exparel groups versus the Old Exparel and New Exparel groups
When examining the inpatient opioid consumption, the data show a statistically significant difference in the number of patients given Hydrocodone (Norco) between the Pre-Exparel (n = 33), Undiluted Exparel (n = 38), Old Exparel (n = 7) and New Exparel (n = 10) protocols (p < 0.0001.) There is a statistically significant difference in the number of patients being given intravenous (IV) Morphine PRN between Pre-Exparel (n = 29), Undiluted Exparel (n = 29), Old Exparel (n = 11), and New Exparel (n = 4) protocols (p = 0.0004). There is a statistically significant difference in the number of patients receiving “as needed” (PRN) Tylenol-3 Tablets (p = 0.0002), but the total number is small enough that it is likely due to factors other than post-operative pain.

There is not a statistically significant difference in the number of patients who were given Dilaudid in the OR (p = 0.3239) or PRN (p = 0.2356) between groups, the number of patients given IV Morphine in the OR (p = 0.6274) between groups, number of patients given scheduled doses of oral (PO) Morphine (p = 0.1620), the number of patients given Fentanyl PRN (p = 0.1177) between groups, the number of patients given Meperidine PRN (p = 0.6525) between groups, the number of patients given scheduled doses of Tramadol (p = 0.3451) or PRN (0.0535), the number of patients given Percocet PRN (p = 1.00), the number of patients given scheduled doses of Tylenol-3 (p = 0.3451), or the number of patients given Fentanyl in the OR which was 100% of patients.

There were no instances of patients receiving PO Morphine PRN, scheduled Meperidine, either scheduled or PRN doses of Oxycodone, or scheduled doses of Percocet. These data are summarized in table 5 on the next page.
Table 5: Opioid Medication usage

<table>
<thead>
<tr>
<th>Opioid Medications</th>
<th>Pre-Exparel</th>
<th>Undiluted Exparel</th>
<th>Old Exparel</th>
<th>New Exparel</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocodone</td>
<td>33 (80.5%)</td>
<td>38 (73.1%)</td>
<td>7 (26.9%)</td>
<td>10 (43.5%)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Dilaudid OR</td>
<td>28 (68.3%)</td>
<td>29 (55.8%)</td>
<td>13 (50%)</td>
<td>11 (47.8%)</td>
<td>0.3239</td>
</tr>
<tr>
<td>Dilaudid PRN</td>
<td>22 (53.7%)</td>
<td>31 (59.6%)</td>
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</tr>
<tr>
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<td>1 (1.9%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0.6274</td>
</tr>
<tr>
<td>IV Morphine PRN</td>
<td>29 (70.7%)</td>
<td>29 (55.8%)</td>
<td>11 (42.3%)</td>
<td>4 (17.4%)</td>
<td>0.0004*</td>
</tr>
<tr>
<td>PO Morphine OR</td>
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<td>0 (0%)</td>
<td>0 (0%)</td>
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<td>Fentanyl OR</td>
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<td>52 (100%)</td>
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<td>23 (100%)</td>
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<td>Fentanyl PRN</td>
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<td>8 (30.8%)</td>
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</tr>
<tr>
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<td>0 (0%)</td>
<td>NA</td>
</tr>
<tr>
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<td>3 (6%)</td>
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<td>0 (0%)</td>
<td>0.6525</td>
</tr>
<tr>
<td>Tramadol Scheduled</td>
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<td>0 (0%)</td>
<td>1 (3.8%)</td>
<td>0 (0%)</td>
<td>0.3451</td>
</tr>
<tr>
<td>Tramadol PRN</td>
<td>3 (7.3%)</td>
<td>5 (9.6%)</td>
<td>5 (19.2%)</td>
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<td>0.0535</td>
</tr>
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<td>0 (0%)</td>
<td>0 (0%)</td>
<td>N/A</td>
</tr>
<tr>
<td>Oxycodone PRN</td>
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<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>N/A</td>
</tr>
<tr>
<td>Percocet Scheduled</td>
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<td>0 (0%)</td>
<td>0 (0%)</td>
<td>N/A</td>
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<tr>
<td>Percocet PRN</td>
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</tr>
<tr>
<td>Tylenol Tablets Scheduled</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (3.8%)</td>
<td>0 (0%)</td>
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</tr>
<tr>
<td>Tylenol Tablets PRN</td>
<td>1 (2.4%)</td>
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<td>9 (34.6%)</td>
<td>2 (8.7%)</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

*Post-hoc pairwise comparisons showed significant differences between the Pre-Exparel and Undiluted Exparel groups versus the Old Exparel and New Exparel groups.
When all opioid consumption is converted into morphine milligram equivalents (MME), the data show a statistically significant difference between the mean opioid consumption of the Pre-Exparel group (100.4 ± 96.9 MME) and both the Old Exparel group (42.8 ± 22.9 MME) and the New Exparel group (66.5 ± 81.2 MME) with a p-value of 0.0002. The data also showed a significant difference in mean opioid consumption between the Undiluted Exparel group (78.6 ± 68.3 MME) and the Old Exparel group (42.8 ± 22.9 MME). It did not show a statistically significant difference between the Undiluted Exparel group (78.6 ± 68.3 MME) and New Exparel group (66.5 ± 81.2 MME). The data show that the use of the Exparel in general results in a reduction of opioid consumption, from a 34% decrease when comparing Pre-Exparel to New Exparel, up to a 57% decrease when comparing Pre-Exparel and Old Exparel groups.

When comparing post-operative length of stay (LOS) in hours and minutes (hh:mm), the data show that the mean difference between LOS for Pre-Exparel (44:41 ± 35:58), Undiluted Exparel (39:07 ± 33:13), Old Exparel (46:36 ± 25:02) and New Exparel (67:26 ± 41:49) is not statistically significant (p = 0.2984). When comparing Total LOS, the data show that the mean difference between LOS for Pre-Exparel (70:20 ± 67:38), Undiluted Exparel (62:54 ± 54:46), Old Exparel (62:27 ± 30:35) and New Exparel (67:26 ± 41:19) is not statistically significant (p = 0.4983). It can be concluded that the New Exparel protocol does not cause a decrease in LOS. This data is summarized on the next page in Table 6 and graphically in figures 9-11.
Table 6: Primary Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Pre-Exparel</th>
<th>Undiluted Exparel</th>
<th>Old Exparel</th>
<th>New Exparel</th>
<th>p-value</th>
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<td><strong>Total Morphine</strong></td>
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<td></td>
<td></td>
<td></td>
<td>0.0002*</td>
</tr>
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<td><strong>Equivalence</strong></td>
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<td><strong>Dose (mg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± Stdev</td>
<td>100.4 ± 96.9</td>
<td>78.6 ± 68.3</td>
<td>42.8 ± 22.9</td>
<td>66.5 ± 81.2</td>
<td></td>
</tr>
<tr>
<td>Median (Q1-Q3)</td>
<td>68.6 (44.6, 116)</td>
<td>58.7 (42.9, 82.9)</td>
<td>36 (25.9, 50.4)</td>
<td>31.4 (20.3, 84.2)</td>
<td></td>
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<tr>
<td>Min-Max</td>
<td>14-509.8</td>
<td>18-426.2</td>
<td>17-105</td>
<td>10-393.2</td>
<td></td>
</tr>
<tr>
<td><strong>Post-op Length</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.2984</td>
</tr>
<tr>
<td><strong>of Stay</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Min-Max</td>
<td>8:31-172:16</td>
<td>8:08-205:54</td>
<td>8:11-97:27</td>
<td>7:11-100:24</td>
<td></td>
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<td><strong>Total Length</strong></td>
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<td><strong>of Stay</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Post-hoc pairwise comparisons showed significant differences between Pre-Exparel and the Old and New Exparel groups, and between the Undiluted Exparel and Old Exparel groups.
Laparoscopic Cholecystectomy with IOC

**Figure 9**

![Box plot showing median total opioid consumption in morphine milligram equivalents in patients who underwent laparoscopic cholecystectomy with intraoperative cholangiogram. Box = 25th and 75th percentile; Bars = min and max values. N = 142 patients; n = 41 in Pre-Exparel, n = 52 in Undiluted Exparel, n = 26 in Old Exparel, n = 23 for New Exparel. Results show significant difference between Pre-Exparel and Undiluted Exparel groups versus the Old Exparel and New Exparel groups. Plots with star showed significant decrease. Outliers trimmed to show detail.]

**Fig 9.** Median total opioid consumption in morphine milligram equivalents in patients who underwent laparoscopic cholecystectomy with intraoperative cholangiogram. Box = 25th and 75th percentile; Bars = min and max values. N = 142 patients; n = 41 in Pre-Exparel, n = 52 in Undiluted Exparel, n = 26 in Old Exparel, n = 23 for New Exparel. Results show significant difference between Pre-Exparel and Undiluted Exparel groups versus the Old Exparel and New Exparel groups. Plots with star showed significant decrease. Outliers trimmed to show detail.

**Figure 10**

![Box plot showing median post-operative length of stay in hours in patients who underwent laparoscopic cholecystectomy with intraoperative cholangiogram. Box = 25th and 75th percentile; Bars = min and max values. N = 142 patients; n = 41 in Pre-Exparel, n = 52 in Undiluted Exparel, n = 26 in Old Exparel, n = 23 for New Exparel. Results show no significant difference in median post-operative length of stay across all groups. Outliers trimmed to show detail.]

**Fig 10.** Median post-operative length of stay in hours in patients who underwent laparoscopic cholecystectomy with intraoperative cholangiogram. Box = 25th and 75th percentile; Bars = min and max values. N = 142 patients; n = 41 in Pre-Exparel, n = 52 in Undiluted Exparel, n = 26 in Old Exparel, n = 23 for New Exparel. Results show no significant difference in median post-operative length of stay across all groups. Outliers trimmed to show detail.
Figure 11

Fig 11. Median total length of stay in hours in patients who underwent laparoscopic cholecystectomy with intraoperative cholangiogram. Box = 25th and 75th percentile; Bars = min and max values. N = 142 patients; n= 41 in Pre-Exparel, n = 52 in Undiluted Exparel, n = 26 in Old Exparel, n = 23 for New Exparel. Results show no significant difference in median total length of stay across all groups. Outliers trimmed to show detail.
**Laparoscopic Appendectomy**

There were 160 total patients who received a laparoscopic appendectomy between January 1, 2012 and August 31, 2017. Of these 160 patients, 3 were admitted to the ICU, 1 patient was pregnant at the time of admission, 1 patient with severe chronic kidney disease, and 1 patient had incomplete records. Out of the remaining 154 patients, 80 patients were male and 74 were female. The average age of the Pre-Exparel group is 36.2 ± 13.6 years, of the Undiluted Exparel group is 36.2 ± 14.5 years, of the Old Exparel group is 44.8 ± 15.1 years, and of the New Exparel group is 37.6 ± 15.5 years. There were 17 patients who presented with perforation of the appendix, 12 patients who presented with gangrenous appendix, and 9 patients who presented with periappendiceal abscess. Other operative findings include 1 patient with bowel malrotation, 1 patient with peritonitis, 8 patients with suppurative appendicitis, 1 patient with tuboovarian abscess, and 16 patients with umbilical hernia. There was 1 patient with bowel obstruction as a postoperative complication. This information is summarized in on the next page in Table 7.
Table 7: Summary of demographic, operative findings, and post-op complications and considerations

<table>
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<tr>
<th></th>
<th>Pre-Exparel (n=60)</th>
<th>Undiluted Exparel (n=49)</th>
<th>Old Exparel (n=18)</th>
<th>New Exparel (n=27)</th>
<th>p-value</th>
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</thead>
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<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at Procedure</td>
<td>36.2±13.6</td>
<td>36.2±14.5</td>
<td>44.8±15.1</td>
<td>37.6±15.5</td>
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<tr>
<td>Male Gender</td>
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<td>20 (40.8%)</td>
<td>11 (61.1%)</td>
<td>17 (63%)</td>
<td>0.2217</td>
</tr>
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<td><strong>Operative Findings</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Perforation</td>
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<td>5 (10.2%)</td>
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<td>Gangrene</td>
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<td>2 (7.4%)</td>
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<td>Others</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<td>0 (0%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Peritonitis</td>
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<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Suppurative Appendicitis</td>
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<td>1 (2%)</td>
<td>2 (11.1%)</td>
<td>3 (11.1%)</td>
<td></td>
</tr>
<tr>
<td>Tuboovarian Abscess</td>
<td>1 (1.7%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
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</tr>
<tr>
<td>Umbilical hernia</td>
<td>7 (11.7%)</td>
<td>5 (10.2%)</td>
<td>4 (22.2%)</td>
<td>0 (0%)</td>
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<td><strong>Post-Op Complications/Considerations</strong></td>
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<td>0 (0%)</td>
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<td>Ileus</td>
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</tr>
<tr>
<td>Peritonitis</td>
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<td>0 (0%)</td>
<td>0 (0%)</td>
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When examining the inpatient opioid consumption, the data show a statistically significant difference in the number of patients given Hydrocodone (Norco) between the Pre-Exparel (n = 43), Undiluted Exparel (n = 31), Old Exparel (n = 5) and New Exparel (n = 6) protocols (p < 0.0001). There is a statistically significant difference in the number of patients being given intravenous (IV) Morphine PRN between Pre-Exparel (n = 31), Undiluted Exparel (n = 20), Old Exparel (n = 4), and New Exparel (n = 0) protocols (p = 0.0004). There is a statistically significant difference in the number of patients given Tramadol “as needed” (PRN) between the Pre-Exparel (n = 7), Undiluted Exparel (n = 5), Old Exparel (n = 7) and New Exparel (n = 5) protocols (p = 0.0383). There is a statistically significant difference in the number of patients who were given Fentanyl PRN between Pre-Exparel (18), Undiluted Exparel (12), Old Exparel (1), and New Exparel (2) protocols (p = 0.0314). There is a statistically significant difference in the number of patients receiving PRN Tylenol-3 Tablets (p = 0.0029) and PRN Oxycodone (p = 0.0132), but the total number is small enough that it is likely due to factors other than post-operative pain.

There is not a statistically significant difference in the number of patients who were given Dilaudid in the OR (p = 0.1245) or PRN (p = 0.8450) between groups, the number of patients given IV Morphine in the OR (p = 0.5148) between groups, the number of patients given PO Morphine PRN (p = 0.2506), the number of patients given Fentanyl in the OR (p = 0.4627) between groups, the number of patients given Meperidine PRN (p = 0.3852) between groups, or the number of patients given scheduled doses of Tramadol (p = 0.1169).

There were no instances of patients receiving scheduled PO Morphine, scheduled Meperidine, scheduled Oxycodone, scheduled or PRN doses of Percocet, or scheduled Tylenol-3. These data are summarized in table 8 on the next page.
<table>
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<th>Opioid Medications</th>
<th>Pre-Exparel</th>
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<th>Old Exparel</th>
<th>New Exparel</th>
<th>p-value</th>
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<td>Hydrocodone</td>
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<td>31 (63.3%)</td>
<td>5 (27.8%)</td>
<td>6 (22.2%)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Dilaudid OR</td>
<td>14 (23.3%)</td>
<td>12 (24.5%)</td>
<td>9 (50%)</td>
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<tr>
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<td>15 (30.6%)</td>
<td>4 (22.2%)</td>
<td>8 (29.6%)</td>
<td>0.8450</td>
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<tr>
<td>IV Morphine OR</td>
<td>2 (3.3%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
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<tr>
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<td>31 (51.7%)</td>
<td>20 (40.8%)</td>
<td>4 (22.2%)</td>
<td>0 (0%)</td>
<td>&lt;0.0001*</td>
</tr>
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<td>0 (0%)</td>
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<td>Percocet OR</td>
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<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>N/A</td>
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</tr>
<tr>
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*Post-hoc pairwise comparisons showed significant differences between the Pre-Exparel and Undiluted Exparel groups versus the Old Exparel and New Exparel groups
**Post-hoc pairwise comparisons showed significant differences between the Pre-Exparel and Undiluted Exparel groups versus the Old Exparel and New Exparel groups
When all opioid consumption is converted into morphine milligram equivalents (MME), the data show a statistically significant difference between the mean opioid consumption of the Pre-Exparel group (60.4±32.9 MME) and the Undiluted Exparel group (46.3±38.1 MME), the Old Exparel group (35.5±17.7 MME) and the New Exparel group (30.4±19.5 MME) with a p-value of <0.0001. The data also showed a significant difference in mean opioid consumption between the Undiluted Exparel group (46.3±38.1 MME) and the New Exparel group (30.4±19.5 MME). It did not show a statistically significant difference between the Old Exparel group (35.5±17.7 MME) and New Exparel group (30.4±19.5 MME). Based on these results, it can be concluded that the use of either the Old Exparel or New Exparel protocol results in a statistically significant reduction of opioid consumption, showing a 50% decrease when comparing Pre-Exparel to New Exparel protocols.

When comparing post-operative length of stay (LOS) in hours and minutes (hh:mm), the data show that the mean difference between LOS for Pre-Exparel (25:11±18:09), Undiluted Exparel (21:11±13:33), Old Exparel (19:40±15:50) and New Exparel (38:37±31:51) is not statistically significant (p = 0.3668). When comparing Total LOS, the data show that the mean difference between LOS for Pre-Exparel (32:56±23:46), Undiluted Exparel (29:44±21:24), Old Exparel (16:21±15:51) and New Exparel (38:37±31:51) is not statistically significant (p = 0.6988). The data show that the New Exparel protocol does not cause a decrease in LOS. This data is summarized on the next page in Table 9 and graphically in figures 12-14.
Table 9: Primary Outcome Variables

<table>
<thead>
<tr>
<th></th>
<th>Pre-Exparel</th>
<th>Undiluted Exparel</th>
<th>Old Exparel</th>
<th>New Exparel</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Morphine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Equivalence</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td><strong>Dose (mg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± Stdev</td>
<td>60.4 ± 32.9</td>
<td>46.3 ± 38.1</td>
<td>35.5 ± 17.7</td>
<td>30.4 ± 19.5</td>
<td></td>
</tr>
<tr>
<td>Median (Q1-Q3)</td>
<td>52.8 (37.8, 79.3)</td>
<td>37 (26.2, 60)</td>
<td>31.7 (25.3, 39)</td>
<td>25 (18.7, 32.5)</td>
<td></td>
</tr>
<tr>
<td>Min-Max</td>
<td>15-154</td>
<td>10-251.5</td>
<td>12.4-90</td>
<td>5-88.2</td>
<td></td>
</tr>
<tr>
<td><strong>Post-op Length</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.3668</td>
</tr>
<tr>
<td><strong>of Stay</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Min-Max</td>
<td>4:33-112:38</td>
<td>7:00-84:01</td>
<td>3:58-73:03</td>
<td>3:38-117:42</td>
<td></td>
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<tr>
<td><strong>Total Length of</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.6988</td>
</tr>
<tr>
<td><strong>Stay</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Post-hoc pairwise comparisons showed significant differences between Pre-Exparel vs all other groups, and between the Undiluted Exparel vs New Exparel groups.
Laparoscopic Appendectomy

Figure 12

Fig 12. Median total opioid consumption in morphine milligram equivalents in patients who underwent laparoscopic appendectomy. Box = 25<sup>th</sup> and 75<sup>th</sup> percentile; Bars = min and max values. N = 160 patients; n = 60 in Pre-Exparel, n = 49 in Undiluted Exparel, n = 18 in Old Exparel, n = 27 for New Exparel. Results show significant difference between Pre-Exparel and Undiluted Exparel groups versus the Old Exparel and New Exparel groups. Plots with star showed significant decrease. Outliers trimmed to show detail.

Figure 13

Fig 13. Median post-operative length of stay in hours in patients who underwent laparoscopic appendectomy. Box = 25<sup>th</sup> and 75<sup>th</sup> percentile; Bars = min and max values. N = 160 patients; n = 60 in Pre-Exparel, n = 49 in Undiluted Exparel, n = 18 in Old Exparel, n = 27 for New Exparel. Results show no significant difference in median post-operative length of stay across all groups. Outliers trimmed to show detail.
Figure 14

Fig 14. Median total length of stay in hours in patients who underwent laparoscopic appendectomy. Box = 25th and 75th percentile; Bars = min and max values. N = 160 patients; n= 60 in Pre-Exparel, n = 49 in Undiluted Exparel, n = 18 in Old Exparel, n = 27 for New Exparel. Results show no significant difference in median total length of stay across all groups. Outliers trimmed to show detail.
Discussion

Modern society has adopted the opiate as the primary method of handling acute and surgical pain, and this has had some grave consequences. A strong indication of the scope of the problem, the United States Government has formally stepped in. On October 26, 2017, President Trump publicly declared the opioid epidemic a “public health emergency.” This means that federal funding will be put forward in an effort to curb the progression of opioid addiction in American communities. American physicians like Dr. Petrey, as well as pharmaceutical companies such as Pacira Pharmaceuticals, are also doing their part in investigating alternatives to opioid analgesia. One such product of this research is Exparel, and the data definitely supports it.

Based on the data analysis, there is a strong suggestion that the use of Exparel in postoperative pain management will result in a significant decrease in mean opioid consumption, from a 26% decrease up to a 50% decrease in the laparoscopic cholecystectomy and laparoscopic appendectomy groups when comparing the New Exparel protocol with Pre-Exparel Protocol. In all three study groups, it appears there is little difference between the New Exparel and Old Exparel protocols, so the decision of which to use may rely more on how much area is to be covered, as more dilution allows for more coverage. There was a significant difference in age in the laparoscopic cholecystectomy with IOC, where it seems that the Undiluted Exparel group is significantly younger than the other three groups. That does not seem to have had much of an effect on the data, however, as there is still a significant difference between the Undiluted Exparel and the Old Exparel group. In practice, using this novel protocol for laparoscopic appendectomies and cholecystectomies will likely have a large effect on postoperative opioid
consumption while an inpatient, which would result in a reduction of opioid related side effects such as nausea, vomiting, constipation, and more serious side effects such as addiction, respiratory depression, and death.

Although there is a significant effect of using Exparel on opioid consumption, it appears that the use of Exparel does not have a significant effect on length of stay. In the laparoscopic cholecystectomy group, the mean post-op length of stay varied by a maximum of 3 hours and 4 minutes between all groups, and 3 hours and 46 minutes for total length of stay. For the laparoscopic cholecystectomy with IOC group, the mean post-op length of stay varied by a maximum of 8 hours and 55 minutes between all groups, and 3 hours and 54 minutes for total length of stay. In the laparoscopic appendectomy group, the mean post-op length of stay varied by a maximum of 9 hours and 8 minutes, and 12 hours and 16 minutes for total length of stay. It is important to note that in the laparoscopic appendectomy group, the data shows that the “Old Exparel” protocol to be most effective when compared to the other protocols. When looking at the graphs, one can see that the data varies in its distribution, but when referencing the mean, it is apparent that there is not much variance between groups.

To summarize, the use of both the “Old Exparel” and “New Exparel” protocols results in a significant reduction in postoperative opioid consumption when compared to the “Pre-Exparel” and “Undiluted Exparel” protocols. Additionally, there is not a significant difference between the “Old Exparel” and “New Exparel” in terms of opioid consumption across all groups.

There are currently plans to incorporate data regarding total hospital cost, but the data analysis is still underway.
CHAPTER VI

CONCLUSIONS

Limitations

The main limitation of this study is that it is a retrospective in nature, which means that only a correlation can be drawn between the use of Exparel and the reduction in opioid consumption or length of stay. Furthermore, there is the potential of pertinent data being unavailable due to incomplete charting or technical problems. For example, a patient may report that they have chronic pain but the nurse may not chart it correctly or at all. I found when reviewing the medication given during the visit, there were instances where the list of medication given in one area of the chart did not match what was given in another area of the chart, or sometimes there was no medication listed at all. These could lead to unintended trends in the data.

Another limitation to this study is that all the laparoscopic appendectomies and cholecystectomies are being performed by Dr. Petrey and various residents, which may cause difficulty in identifying and controlling for confounding variables, such as the skill level of the resident. However, Dr. Petrey was presiding over every one of these surgeries, as well as performing the periportal or modified TAP anesthesia on all patients, which would ensure a certain level of quality. Furthermore, neither the patient nor the surgeon was blinded as to which treatment they were given, so that may affect the results slightly.

Another limitation is that there is not any reliable way to measure opioid consumption after the patient is discharged, and would largely be based on self-reporting and there would most likely be significant loss to follow up, leading to incomplete or unreliable data.
Future Directions

The best way to improve the quality of the data when comparing Exparel to other protocols is to use it in a prospective study. Based on the findings of this study and previous studies I have reviewed, it may not be wise to compare using 0.5% Marcaine to Exparel considering Exparel has already shown to have a significant effect in reducing opioid consumption, unless use of Exparel is contraindicated. It may be better to compare different mixtures of Exparel to each other to see if there is an optimum mixture.

In terms of measuring opioid consumption, it would be interesting to split up preoperative and postoperative opioid consumption to see if there is a significant difference. Also, in addition to measuring inpatient opioid consumption, the patient can also be asked to give subjective pain scores on a Wong-Baker scale, recording the time the scale was taken with the intention correlating it with opioid consumption. Furthermore, the patients could be polled after discharge to monitor their subjective pain scores and consumption of opioid and non-opioid pain medication. If prescribed opioid medication for home, they could also be asked if they experienced any opioid related side effects such as nausea or constipation. Additionally, it would be interesting to see if there is an effect on the time away from work or other normal activities when comparing people who received Exparel and those who did not. Differences in racial or ethnic backgrounds could be incorporated as well.

Another way to ensure generalizability of the data would be to gather data across multiple sites, or across multiple attending surgeons. This would help to increase external validity and serve to show that it is actually that specific dilution of Exparel that is causing the analgesic effect.
CHAPTER VII

REFERENCES


35. “Opioid Overdose.” Centers for Disease Control and Prevention, Centers for Disease Control and Prevention, 30 Aug. 2017


CHAPTER VIII

INTERNERSHIP EXPERIENCE

My internship was completed at Baylor University Medical Center in Dallas, Texas in the Department of Trauma Research. I performed my research under the guidance of Dr. Laura Petrey as the Principal Investigator, Mackenzie Dome and Evan Rainey as the Clinical Research Coordinators. The studies that I participated in include:

I. Nurse-driven chest tube management protocol: Let’s get the chest tube out more quickly and safely? (CT Protocol) (dropped)

II. Evaluation of the incidence of venothromboembolic events in traumatic brain injury patients before and after implementation of an evidence based algorithm for chemical prophylaxis (TBI VTE) (dropped)

III. Aortic Trauma Foundation Blunt Thoracic Aortic Injury (BTAI)

During my internship, I performed the following duties:

1. IRB Submissions
   a. New study applications
      i. Form 15
      ii. Form 34
      iii. Form 18
   b. Continuing review
   c. Change in key personnel
   d. Protocol amendment
2. Submission to Surgical Peer Committee
3. BHCS research funding request
4. Attending meetings/conferences
   a. Weekly office meetings
   b. Weekly trauma conference
   c. Grand rounds
   d. Attend ICU multidisciplinary rounds
5. Submission of research to Southwestern Surgical Congress and NTACS
6. Assist with other studies (BTAI, CT Protocol, VTE)
   a. Literature review
   b. Protocol development
   c. Data entry
   d. Patient enrollment
   e. Organization of regulatory binders
7. Escorting therapy animals

Journal Summary

For the first few months, my days typically began with me screening patients for the chest tube study, reviewing their charts in AllScripts to determine if they fit the inclusion criteria. It was interesting to note that I did not find a single person the entire time, as they were usually outside of the inclusion window. We ended up dropping that study due to low enrollment. Eventually I started work on data entry for the BTAI study, which ended up being a pretty time intensive and very thorough. A typical day for me was spent on chart review and data entry,
building regulatory binders, doing continuing review on iRIS, and other lesser tasks. Weekly events included staff meetings and conference calls, rounds, trauma conference, and therapy dogs.
Appendix A: Daily Journal

Daily Internship Journal

5/30/17
I started my day by going to the ICU on 7 Roberts to do rounds with Dr. Petrey and a handful of students, interns, and other staff. Dr. Petrey used this opportunity as a teaching experience for everyone, explaining the connection between people who use a significant amount of chloroseptic spray and methemoglobinemia, as well as the common symptoms and the best treatment. Afterwards, we had a lunch meeting with the representative from EHOB about their new device for identifying unhealthy tissue and preventing necrosis. After that, I attended a research meeting regarding the current and upcoming studies, after which I finished my CITI training.

5/31/17
I arrived early to get both my badge and my parking pass from transport services. I did rounds again in the ICU on 7 Roberts with Dr. Weddle. I returned to our office and talked with Evan about the four areas of research that Dr. Petrey participates in: damage control laparotomy, chest tubes and adverse events, testing Exparel as an effective anesthetic, and blunt trauma aortic injuries.

6/1/17
Today started off with rounds again with Dr. Petrey. One of the more interesting cases involved the relationship of vitamin K2 with hyperbilirubinemia and kernicterus in an infant.
Afterwards, Mackenzie showed me how to screen patients for the chest tube study for Dr. Petrey, which I helped with under her supervision. Evan showed me an example of how they performed a literature review so that I could get started on that, which I did for the rest of the day.

6/5/17

I spent the morning learning all the ins and outs of the chest tube study with Evan, such as the study objectives, inclusion and exclusion criteria, subject recruitment and screening, study procedures, and how to record and handle data. Then we had a fall meeting discussing the research grant we had received and how to allocate those funds, as well as reviewing the applicants for the new research position. I followed up with my literature review after that.

6/6/17

I started the morning screening for the chest tube study under the guidance of Mackenzie, followed by a trauma conference. In the conference, we talked about the protocol regarding when to do a craniotomy following acute brain injury. Following that, we had an office meeting regarding the progress of all the studies currently being run. I was assigned to with the blunt traumatic aortic injury study as well as with the chest tube study in various capacities. I worked on my literature review the rest of the day.

6/7/17

I tried to start screening for the chest tube study but I did not have access to the EMR system, AllScripts. I called IT and they said that I needed a request for access from the CRC from my department or my department head. As it turns out, I wasn’t allowed to access patient charts yet for the chest tube study yet because I haven’t yet been accepted by the IRB to be added to study personnel. Since I wasn’t able to help with the projects, I worked further on my literature review for my project.

6/8/17

I worked on my literature review for most of the day, but I also went to grand rounds at noon in the main hospital. The topic of discussion was temperature/fever management in
patients with acute brain injuries. They found that a person with a sort of brain injury would have a much better outcome if their temperature was kept below a certain point, as for every degree increase in Celsius, the brain consumes approximately 13% more resources in the form of nutrients and oxygen. Logically, the inverse is true as well, so the goal is to keep someone’s temperature as low as possible without compromising other organ systems. Additionally, the presenter went into detail regarding the fact that once the body reaches a certain temperature, it resets the normal point so that even though a person can have a high fever, they will feel cold and start to shiver. The shivering increases body heat further and can place additional risk on the patient.

6/9/17
One of the clinical research assistants and I chaperoned the volunteer and his therapy dog, Quinn. We traveled to the ICU in Roberts, med surg in Truett, and then back to the transplant care floor in Roberts. We didn’t get to see as many patients as normal, as most of them were either in a procedure of some kind or pretending to be asleep, but there were several who were very happy to interact with Quinn. After this, I worked on my literature review for my project.

6/12/17
Today we chaperoned the therapy dog, Besa, and her owner to Roberts ICU and transplant care floor, as well as med surg in Truett. We saw some of the same patients, but we saw mostly new ones. Afterwards I worked on my literature review, but I had to leave early to fill out some paperwork.

6/13/17
I started off today by taking a couple volunteers to rounds in the Roberts ICU, after which we had a trauma conference where they talked about the accuracy of certain types of measurements of arterial vs. venous pressure as well as the relationship with positive pressure respiration and how it affects blood pressure. After that we had an office meeting regarding the progress made on a number of projects, as well as status updates from other sites. The volunteers and I started making traumatic brain injury (TBI) information packets for families of
those who suffer a TBI so they don’t have to google what it is or what they should be concerned about.

6/14/17

Today I spent the morning screening for the chest tube study under the supervision of Mackenzie. Unfortunately, we didn’t find any patients that fit within the inclusion/exclusion criteria. I spent the rest of the day working with the excel sheet that Mackenzie designed for the BTAI study, trying to figure out why the file size was so huge. The goal was to get the file size low enough that it could be shared between people through the network rather than using physical copies.

6/15/17

I started today with screening for the chest tube study after I worked with IT for about an hour trying to get allscripts access onto the laptop that I am using. Again, I didn’t find anyone who fit the specific criteria, but some were close. After this, I started working on the BTAI excel worksheet and made some headway. Apparently one of the sheets was absolutely gigantic for no reason, so I just copied and pasted the text onto a new sheet and it fixed the problem.

6/16/17

I started today with screening for the chest tube study, followed by reviewing the protocol for patient inclusion/exclusion criteria the BTAI study. Our goal was to start construction of a central database for all patients over the past year who had blunt thoracic aortic injury for further study. I worked on my sheet that I’m going to use for my advisory committee meeting this coming Monday and reviewed with both Evan and Mackenzie.

6/19/17

I started out with screening for the chest tube study, but didn’t find anyone that fit the criteria. I also started going over my material for my advisory committee today, but then the
meeting was canceled. I finished up working on the data sheet for the BTAI study, and submitted it to Mackenzie for review. I requested patient data from Jake based on ICD10 codes and inclusion/exclusion criteria, of which we found 17 potential patients. After this, I started work on my research proposal, and hope to have it done by Wednesday of this week.

6/20/17
I went over the excel sheet for the database for the BTAI study just to double check it, and after that I spoke with Jake and asked him to pull patient records that fit within the specific ICD9 and 10 codes that correlate with blunt traumatic aortic injury. I slowly but surely navigated the datasheet and correlated it with the charts to fill it out, with some edits and changes. We went to a meeting regarding HIPAA where the speaker discussed the laws regarding patient privacy and health information, as well as posed examples where someone breached a patient’s privacy even though they thought they were in the right.

6/21/17
I screened for the chest tube study this morning, but we had to change the way it was performed due to concern for HIPAA compliance. After this, I did further work on the BTAI study, finishing the data input for one patient. I asked Mackenzie to review my data input so I could be sure that everything that was supposed to be done was done correctly. I started work putting together the regulatory binder for the BTAI study, but I did not quite finish that. I was missing some key documents so I will have to find where they are located first.

6/23/17
I started today by working with the therapy dogs, Quinn and Gina, and went to 6 Truett and 4 Roberts. Soon after we got back to our office, we had to leave to put on our moulage to participate in the training and testing of the new trauma surgery residents.

6/26/17
Started today with screening for the chest tube study, but didn’t find anyone that fit the criteria. I had a meeting with Dr. Petrey at 11:30 where we talked about the Exparel study and its goals and protocol. During the meeting, it became apparent that there are some issues with the IRB approval for the Exparel study. We spoke briefly about alternatives if the IRB doesn’t
approve this particular study. After this, I drove back to UNTHSC to have a meeting with Dr. Mathew to discuss what my options are.

6/27/17

This morning I screened for the chest tube study, but again didn’t find anyone who fit the inclusion criteria. I also continued the construction of the BTAI database, adding another complete patient. We had an office meeting after this where we discussed the future of some of the projects, as well as the problems with the Exparel study IRB approval. Afterwards I continued my work on the BTAI database.

6/28/17

Today I started with the BTAI database, and we had a short meeting regarding the status of the Exparel IRB approval. Turns out that it would be easier to rewrite the protocol and reapply to the IRB, so that is what I will be mostly working on today. My goal is to rewrite the protocol with the correct explanations of the appendectomy and the cholecystectomy, make a rough timeline defining the three cohorts of the study, as well as making a couple diagrams showing how the surgeries are performed.

7/3/17

Today I was the only one at the office, so I mostly worked on my research proposal seeing as I couldn’t screen for the chest tube study. I conferred with Dr. Powers and had him look over what I had on my proposal thus far.

7/5/17

Again, I started with screening for the chest tube study, as well as coordinated the advisory committee meeting that is scheduled to happen tomorrow at 8am via Skype. I also finished the last of my edits to my research proposal and submitted it to Dr Simecka for a final review.

7/6/17
We had our advisory committee meeting this morning, where we went over my research proposal and I was informed of any problems or suggested edits that I need to make. The largest problem turned out to be my statistical analyses section, in that I needed to define what variables I am using as well as be more explicit in my explanation of what statistical tests will be employed. I spoke with Dr. Powers for a couple hours after the meeting, then followed up with data input for the BTAI study.

7/7/17

I started today by screening for the chest tube study, but again there weren’t any patients who fit the criteria. Also, we didn’t have to do the dogs like we usually do on Fridays. I worked with Mackenzie a little bit more on my research proposal, and she explained how the surgical peer review system works, and gave me some examples on how to submit to the surgical peer review committee. I worked on that the rest of the day.

7/10/17

Against started with screening for the chest tube study, and again no patients fit the criteria. I then continued work on my revisions for my research proposal and submitted it to Mackenzie and Dr. Petrey to review.

7/11/17

Started with chest tube screening, then went to the trauma conference where they talked about the effects of multidisciplinary rounds and obligatory consult. They showed that the morbidity rate and mortality rate decreased with either or both of those institutions present. Additionally, they talked about the effects of having an intensivist as the attending for the ICU rather than having other specialists such as hospitalists. After that, I finished entering the data for the last case of the BTAI study. We had a research meeting with Dr. Petrey where we talked about some small changes that could be made to my proposal and protocol.

7/12/17

I still didn’t find anyone that fit the criteria for the chest tube study. There were a couple people who received chest tubes for pneumo/hemothroax but they were still outside of our 4.5
hour inclusion window. I also noted that there have been a couple times where a patient should have shown up on the trauma database and would have fit all of the inclusion criteria but for some reason they didn’t show up until the following day. We decided that the best course of action is to record when these kinds of things happen so we can look into it.

7/13/17

Screened for the chest tube study, but didn’t find anyone. I finished up my draft for surgical peer review, and I submitted it to Evan and Mackenzie for editing. The due date for turning these in is tomorrow, but I think the actual meeting is next Thursday.

7/17/17

Started screening for the chest tube study, then I did some edits on my research proposal based on feedback from Dr. Petrey, Dr. Simecka, and a handful of suggestions from one of Dr. Petrey’s peers. They suggested to eliminate ICU patients from the study seeing as they are sick enough to be in the ICU their length of stay will most likely not be determined by the type of analgesic they receive. Additionally, they suggested to look at postoperative length of stay rather than total length of stay, considering the days before the surgery would not be affected by which local anesthetic is used.

7/18/17

I screened for the chest tube study, but didn’t find anyone. We had a potluck lunch to celebrate the newest employees, Riley and Estrella, starting work here. I had to drive to the nearest Kroger to buy some food to bring. After the potluck, we had our research meeting where we touched base with everyone on their respective progress. After this I worked on the IRB application a bit more, as well as made some edits to my paper I submitted for surgical peer review to make it answer the questions that needed answering.

7/19/17

Again, started with screening for the chest tube study. There was one person who had a pneumothorax, but the attending elected to let it resolve on its own rather than using a
thoracostomy tube. I doubled checked later in the day just to be sure, but there were no changes. After that I did some minor adjustments on my research proposal, as well as my surgical peer review paper.

7/20/17
I started with screening for the chest tube study, and again didn’t find anyone. I emailed back and forth with Dr. Petrey regarding changing my inclusion/exclusion criteria on my Exparel study and what she is looking for in the end game. I ended up choosing to change ICU stay as part of the exclusion criteria as well as focusing primarily on postoperative length of stay and cost versus total length of stay and cost.

7/21/17
Started with the chest tube study again, then I worked on the IRB submission form through iRIS using IRB forms from old studies as a reference. Apparently, they have updated the form so now there is an entire section related to form 1, or the summary of the protocol of the study. We also had a meeting with some of the other research members that I had never seen before. We talked about a recent survey of employees and the various facets of their job satisfaction. I left soon after that meeting was over.

7/24/17
Did a quick screening for the chest tube study, as there were only a couple recent trauma patients admitted to the ICU within the past few days. No one with a pneumo/hemothorax or chest tube. We had a quick meeting with Mark regarding the results of the surgical peer review meeting last Thursday, and I got some feedback on my Exparel study that I’m working on.

7/25/17
This morning I screened for the chest tube study, and there was one person who had small pneumothorax but they elected to not place a chest tube. Today I had to leave early to drive to campus to gather signatures from my advisory committee and department head.

7/26/17
Today I started with screening for the chest tube study, then I worked on my IRB application form. I had Mackenzie look over it to see if there were any major problems. Also, we had a research meeting at 1:15 where we talked about the state of our current studies. We talked about starting a new study investigating the relationship between seatbelts, airbags, and facial fractures. We also touched base with the Exparel study. After that we had a meeting with some people from the trauma and emergency departments.

7/31/17
I screened for the chest tube study this morning, still didn’t have anyone fit the criteria. I spoke with Jake about the plan with the airbag/facial fracture study, and apparently the exact study that we were planning on doing had already been done last year. If we were to do it again, 2013 would be the only new data. I also spoke with Dr. Powers about this, and it seems as though the best course of action would be to just scrap the idea rather than spend the time writing the study for only one extra year of data.

8/1/17
Screened for chest tubes, there was one person that fit the criteria but they were outside the study window unfortunately. I spent a little bit of time looking into the airbag/facial fracture study to see if we could redo the study while addressing the limitations that they listed. After this, we all went to the trauma conference which was led by Dr. Foreman. He spoke about whether and when to use alpha or beta agonists/antagonists based on the condition of the patient.

8/2/17
Screened for the chest tube study, and again I found someone who may potentially fit the inclusion criteria. The had a pneumothorax but haven’t had a chest tube placed yet, so I will keep my eye on that patient to see if anything changes. After this I went over some of the details in the datasheet of the BTAI study with Mackenzie, and it was sent off to Dr. Shutze for review.

8/4/17
Since Mackenzie was out of the office today, I wasn’t able to screen for the chest tube study. Instead, I worked on my IRB submission for my study. I was able to finish almost all of
the details and now that I received the approval from surgical peer, all I have left to do is have the office administrator sign form 34, then I can submit to IRB. I prefilled out form 34 and then forwarded it to Kris Chionh, our office administrator, to sign.

8/7/17

This morning I started off with speaking with Dr. Powers about number of things, including networking with Dr. Ann Marie Warren and Dr. Biggs. Afterwards, I did some literature review on the topic of MVCs and facial fractures. I reviewed some more related studies for inspiration, and it seems as though, if we pursue this, that may be wise it incorporate soft tissue damage and/or neck injury on top of facial fractures.

8/8/17

Started today with screening for chest tube, but didn’t find anyone. We had trauma conference today where the topic was on types of ventilators and what settings to use on the ventilators. The speaker also talked about what to look out for certain patients, such as patients with problems with lung elasticity such as those with COPD. After this, I continued my literature review for the MVC study.

8/9/17

Started today with chest tube screening. I had a couple people who had chest tubes placed but none of us were here to consent them as it happened late last night. I found some good articles regarding soft tissue injury and neck injuries due to airbags, but I’m still not sure if there is enough information here to continue pursuing the topic. We submitted the data that we have accrued for the BTAI study for review, but it is a little bit too early to really do anything with the data since we only have 8 subjects.

8/10/17

Chest tube study again, followed by continued literature review for the MVC study. I also spent some time speaking with Dr. Powers for the purpose of making an appointment with Dr. Warren and Dr. Biggs. After this, we went to grand rounds which was hosted by Dr. Foreman. He talked about using each other as medical professionals to find support, as well as
finding ways to increase your own resilience. Apparently, physicians in the ICU have the
highest burnout rate, followed closely by emergency specialists. What he said really resonated
with me as I have some experience in critical care and have witnessed some pretty traumatic
things, but I can only imagine what it must be like to have to face such things every day.

8/11/17

I spent the morning with Quinn the Leonberger therapy dog. We spent some time on 6
Truett med surg, 7 Roberts ICU and 4 Roberts transplant floors. After this, we received the
feedback on the BTAI datasheet from Dr Schutze, and we ended up excluding one of the patients
because they were a transfer from another facility, thus reducing the number of subjects to 7.
There is a section on the datasheet that pertains to related thorax injuries, and I had a question
about whether to include results found by the medical examiner versus only the initial
radiographs. Dr Schutze said to only include the radiograph data in that section. I continued my
literature review for the MVC study.

8/14/17

Started with the chest tube study again, and still didn’t have anyone that fit the criteria.
We received notice that we have to do the continuing review for the BTAI study, so I worked
with Mackenzie on that. I finished most of it, but there were a couple parts that I wasn’t quite
sure how to answer.

8/15/17

I started with chest tube screening, had two people who received chest tubes late last
night, so we weren’t there to consent them. After this, I worked some more with Mackenzie on
the BTAI continuing review and finished/submitted it. We had a staff meeting with everyone
where we talked about the ongoing status of everyone’s studies. We talked about another project
that Jake is working on that I could be a part of, but I can’t remember what it was. I will have to
ask him later.

8/16/17
Chest tube screening, followed by corrections proposed by the IRB initial review. All I had to change was adding the IRB number, date, and version number onto the protocol page, as well as change the exclusion criteria to anyone younger than 18 years old instead of 16 years old. I revised my protocol form and resubmitted.

8/17/17

Started with screening for chest tubes; didn’t find anyone who fit the criteria. We received notice that apparently, we need to fill out the BHCS departmental research support form, which deals with departmental funding and finances. That form has to be filled out and signed by both Dr. Powers and Dr. Petrey before my study submission is actually reviewed by the Baylor IRB.

8/18/17

I started today going over to 6 Truett with Riley to meet with Rover the therapy dog. We went to the ICU in Truett and Roberts, followed by the transplant floor in Roberts. Afterwards I screened for the chest tube study. Apparently, we had missed someone with a hemothorax who would have fit the inclusion criteria because whomever is in charge of updating the trauma log must have missed that particular person.

8/21/17

Started today screening for the chest tube study. Again, we had someone who was really close to meeting the inclusion criteria. He was of the appropriate age and was within the screening window, but apparently, he had been transferred from another hospital which is one of the exclusion criteria. For our lunch break, we went out to garage 4 and observed the solar eclipse for a while. I also finished the BHCS form for my study and submitted it to Miranda Mendoza to sign off on.

8/22/17

Started this morning again with chest tube screening, and didn’t find anyone who fit the criteria. I received notice from Miranda that she signed off on the BHCS funding form, so as far as I know that is the last piece of the puzzle for the IRB approval of my study. Miranda said that
I should hear back by the end of this week whether or not my study has been approved. We all went to the trauma conference after this, followed by our weekly office meeting. I finished the day reviewing some of my old sources to see if there was anything else I could add to my background.

8/23/17

Found out this morning that my Exparel study was approved by the BUMC, so at this point my main objective is to get all of the required forms together to submit to the UNTHSC IRB so I can start working with my data. I worked on the chest tube study, and actually had a couple people with chest tubes, but none of them fit the inclusion criteria, as one was a transfer and one was outside of the age range. I spent the rest of the day filling out, signing, and scanning my required forms and double checking with Dr. Mathew what I need to submit.

8/24/17

Started off today by continuing screening for the chest tube study. I didn’t find anyone, so I spent the rest of the day designing my database for my study. Most of my time was spent finding the patient’s MRN’s from their name and date of birth.

8/25/17

Worked with the therapy dogs Gina and Quinn this morning. We went to 6 Truett, 7 and 4 Roberts. Afterwards, I spent the rest of the day entering data into my database.

8/29/17

Started by screening for the chest tube study, and we missed one person who wasn’t on the trauma log for some reason. Afterwards, we all went to the trauma conference. The speaker’s topic was focused around the indications, strategies, and risks of intubation. Then we had our office meeting where we talked about all of our projects, which I followed up with data entry for my study.

8/30/17

Screened for the chest tube study, but didn’t find anyone who met criteria. I had a meeting with Dr. Petrey to have her go over my database to see if there was anything critical that
was missing from it. She gave me a bunch of suggestions for data points that I should consider, and I made those edits database based on her suggestions.

8/31/17

I screened for the chest tube study again, and again didn’t find anyone that satisfied the criteria. After this, I had a meeting with Dr. Powers, followed by data entry for my study.

9/1/17

Spent a bit of time screening for the chest tube study, followed then by more data entry. We all left a little bit early today to have our ‘going away party’ for Mackenzie at E Bar.

9/5/17

Spent the first couple hours of my day entering data on my study, made a few changes to my database, and then went to trauma conference where they talked about CLABSI, or central line associated bloodstream infection. My coworker Jake also had his presentation at the end. I did more data entry until I left for the day.

9/6/17

Today we decided to drop the chest tube study, as it wasn’t getting the turnout that it needed. As far as what I worked on today, it was pretty much only data entry. I have a lot more data than I thought.

9/7/17

Spent the entire day today only doing data entry. Nothing out of the ordinary or exciting.

9/8/17

Had the leonbergers today, Quinn and Gina. Then just did data entry until I had a meeting with the pharmacist Jennifer Roth about my database and how best to find the data points that I’m looking for, as well as seeing if there is potentially a pharmacy student that may want to help out with the research to get their name on something.
9/11/17

Only did data entry today. Didn’t have much time for anything else.

9/12/17

Started with more data entry, and messed around with my data sheet a little bit to make it easier to read. Then we had trauma conference going over CLABSI again. I worked on data entry for the rest of the day after this.

9/13/17

Finished a couple more years worth of patients on my data sheet, then I had a meeting with Dr. Petrey where she advised me on my database and what data points I should be looking for. I had to go back to some previous patients to make some changes, but it didn’t take too long.

9/18/17

Worked on data entry some more, then had a meeting with Lauren Baskett, a pharmacy student who expressed interest in jumping on the study to help. She has research experience before, especially regarding opioid consumption so she should be very helpful. Now I have to get her set up with an iRIS account and approved by the IRB so she can start working.

9/19/17

More data entry today, and I also had a meeting with Jennifer Roth again to talk about the other kinds of medication that can be given as an alternative to opiates, as well as other considerations when it comes to medication given.

9/20/17

Only data entry today. Nothing else of note.

9/21/17

Still just data entry. I’m still pretty far behind but I’m starting to catch up a little bit.
9/22/17
Had Quinn the therapy dog this morning, but no Gina. I then spent the rest of the day entering data.

9/23/17
Came in on the weekend to catch up some more on my datasheet.

9/24/17
Came in on Sunday too, and I finished the lap chole sheet, or at least enough to get case matching.

9/25/17
Only data entry today. Nothing too exciting.

9/26/17
Did some more data entry this morning, then went to trauma conference where they talked about how to handle intracranial hemorrhage and strokes, and what tools to use and what methods are most effective for reducing incidence of physical deficits for those patients. After this I continued with my data entry.

9/27/17
Did some data entry, and then had a lunch meeting with some of my CRM compadres.

9/28/17
Did some more data entry today, but I also had to do a little bit of work on my secondary application for Texas A&M to get it submitted.

9/29/17
Did some data entry today, and I got a call from TCOM asking me to come in for an interview, so I was too excited to do any more work that day. Kind of a mistake but it’s fine.
10/1/17
I came in on Sunday to make some more headway in my data, but unfortunately developed a migraine so I wasn’t able to work very long.

10/2/17
I spent a large portion of my day catching up on my journal, as it had been a long time since I last updated it. After this, I worked on data entry until 9pm.

10/3/17
I did data entry in the morning until trauma conference where they talked about considerations when dealing with a gravid patient. After this we did walk with a doc along the track behind Pickens hospital, followed up by more data entry.

10/4/17
Just data entry, stayed until 9.

10/5/17
Started today with data entry, had a short meeting with Dr. Petrey about my data, followed by even more data entry. I ended up staying late again.

10/6/17
Did some more data entry, went to Freshii with Evan, Riley, and Estrella, and then more data entry.

10/8/17
Came in on Sunday, stayed until midnight.

10/9/17
Spent the morning doing even more data entry, then had a meeting with Monica the statistician about how we are going to go about analyzing this data, as well as seeing if there was any way I could make her job easier.
10/10/17
I went to UNTHSC to meet with Dr. Simecka and turn in forms to Carla.

10/11/17
Even more data entry, and then another short meeting with Monica.

10/12/17
FINALLY FINISHED ENTERING MY DATA. Time to celebrate by sending it off to Monica.

10/13/17
Worked with Quinn the therapy dog this morning. Quinn is the best. Had a quick meeting with Monica again and then did some literature review for my thesis to fill in some gaps.

10/16/17
Did some literature review for my thesis, and did a little bit of work on it as well.

10/17/17
Did a bit of literature review, then went to trauma conference where they talked about 3 case studies from the ICU on 7 Roberts. Then had an office meeting after this.

10/18/17
Did some work on my thesis, followed by moulage for the ATLS training. Apparently, we are training the judges this time.

10/19/17
More work on my thesis, met with Dr. Petrey about the data again, followed by more ATLS moulage.
Did some more work on my thesis, and then another short meeting with Dr. Petrey, where we talked about the potential of fitting in total hospital cost into my study after I finish my thesis.

10/21/17
Came in on Saturday to work on my thesis, and got the last bit of data.

10/23/17
Had a mock interview today at UNTHSC, met with my advisor, and then worked on my thesis.

10/24/17
I worked on my thesis this morning, then went to trauma conference where they talked about under what circumstances to give fluid resuscitation, as well as alternatives to giving fluids that can increase stroke volume. We then had an office meeting, followed by more work on my thesis. I found that there were some screwy things with my data, so I spoke with Monica to try to figure out what is going on. I finished a decent draft of my thesis today, and I sent it to Evan and Dr. Simecka for some preliminary feedback.

10/25/17
Spent the morning working on my thesis, trying to get the graphs to work. I’ve been having some trouble getting excel to make my graphs without crashing. I also had a meeting with Monica again to talk about the statistical analysis and some errors in the data that we needed to fix. Had a short meeting with Evan and talked about some revisions for my thesis. I suppose I’m pretty much done with my thesis except for the graphs.

10/26/17
I worked some more on my thesis, then had a quick meeting with Jake to have him help me with my graphs. It turns out that you can’t really do the graphs that I wanted to do in excel, so he had to use his own statistical program to make the graphs. They are much better than I thought they would be.
10/27/17

Had therapy dogs this morning with Quinn and Gina, then I worked on my thesis. I’m submitting to my committee today.
Appendix B: Approval Letters

July 30, 2017

Dear Dr. Petrey MD:

Regarding your proposal: Pain Management after Appendectomy and Cholecystectomy: An Innovative Protocol using Exparel

Principal Investigator: Laura B. Petrey MD
Core Team: Mark Powers, PhD; Evan Elizabeth Rainey, MS, CCRC; Mackenzie Dome, MS, CCRC; Pete Newman

The Surgical Research Peer Review Committee of the Department of Surgery at Baylor University Medical Center met and reviewed your proposal on July 20, 2017. The committee has approved the scientific merit of this proposal and has asked Tammy Fisher, RN, to forward this information to you so the proposal can proceed to the Baylor IRB.

The committee did have some concerns with the actual construct of the study. These are meant for consideration and do not detract from the scientific merit of the study.
- Two reviewers had questions regarding how length of stay will be calculated. It would seem that post-operative LOS may be a better calculation than total hospital LOS.
- Consider excluding ICU patients or at least trying to identify a less diverse patient base.
- Are these from a practice database or will these be by hospital/Eclipsys review?
- In terms of quantitating opioid use, many investigators will involve a pharmacist in the study.
- Hospital opioid use can be measured, but with many of these patients having such a short post op LOS, how will outpatient opioid use be determined. Other studies have found this very challenging.
- If patients do have a significant post op LOS and opioid use can be measured and compared, would this not be a sicker and more complex patient set in whom opioid use alleviated by Exparel is less significant.

Good luck on your study.

Sincerely,

John T. Preskitt, MD FACS
Chair, Surgical Research Peer Review Committee
Baylor University Medical Center, Department of Surgery
STATEMENT OF CHIEF OF SERVICE/CHIEF SCIENTIFIC OFFICER

(This person can be anyone who has the scientific knowledge to approve the validity of the proposed study. The PI is not authorized to sign this form as this creates a conflict of interest.)

Project Title: Pain Management after Appendectomy and Cholecystectomy: An Innovative Protocol using Exparel

IRB #: 017-

Principal Investigator: Laura Petrey, M.D.

Name and Title of Scientific Review Delegate: John Preskitt, M.D.

I have reviewed this proposed research project and my signature below certifies that this project has scientific and scholarly validity. My signature also certifies that this project has undergone scientific and scholarly review to determine that it has scientific or scholarly validity. I also certify that conduct of this project is in compliance with the mission and goals of Baylor Health Care System and this service.

[Signature]

Signature of Chief of Service/Medical Staff Delegate/Chief Scientific Officer

[Signature]

Date of Signature: 7-20-17
IRB Approval – Expedited Review of New Study

To: Laura Bruce Petrey, MD

Copy to: Laura Bruce Petrey, MD, Mackenzie Dome, Pete Newman

Date: August 16, 2017

Re: 017-245
Pain Management after Appendectomy and Cholecystectomy: An innovative protocol using Exparel Reference Number: 301865

Your new proposal was reviewed by a designated member of Baylor Scott & White Research IRB Red via expedited review. This study was determined to be eligible for expedited review as it involves no greater than minimal risk to the subjects and fits into the following category(ies) from the 1998 approved list: Category 5: Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis)

This review included the following components:

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<th>Study Application</th>
<th>Outcome</th>
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<tr>
<td>Form Name</td>
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<tr>
<td>Study Application - Review by BRI IRB</td>
<td>Approved as Presented</td>
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<th>Study Document</th>
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<td>Version 1.0</td>
<td>08/16/2017</td>
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<td>Signed form 18</td>
<td>Version 1.0</td>
<td>08/04/2017</td>
<td>Approved</td>
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Your submission has been approved. The approval period begins on 08/16/2017 and expires on 08/15/2018. Your next continuing review is scheduled for 06/15/2018.

This study is approved to be conducted at the following locations:
Baylor University Medical Center, Main, BUMC-Trauma Center

The following individuals are approved as key study personnel (research team members & administrative support):
Buckner, Robin; Dome, Mackenzie; Newman, Pete; Petrey, Laura Bruce, MD; Powers, Mark, PhD; Rainey, Evan Elizabeth, MS; Roth, Jennifer M
Based on the information provided in your submission, the IRB has determined that this study qualifies for a waiver of informed consent in accordance with 45 CFR 46.116 (d) and a waiver of HIPAA Authorization 45 CFR 160 and 164.

All events that occur on this study including protocol deviations, serious adverse events, unanticipated problems involving risks to subjects/others, subject complaints or other similar events must be reported to the IRB in accordance with the respective policies. Remember that this study is approved to be conducted as presented. Any revisions to this proposal and/or any of the referenced documents must be approved by the IRB prior to being implemented. Additionally, if you wish to begin using any new documents, these must receive IRB approval prior to implementation of them in the study.

IRB approval may not be the final approval needed to begin the study. All contractual, financial or other administrative issues must be resolved through Baylor Scott & White Research Institute prior to beginning your study.

For Investigator Initiated studies that meet the requirements to be posted on www.clinicaltrials.gov; as Principal Investigator, it is your responsibility to ensure that your study is listed prior to enrolling the first subject. Instructions on fulfilling this requirement can be found in iRIS under the “Help” tab.

If you need additional assistance, please contact the IRB Specialist at 214-820-9989 (NTX) 254-771-4836 (CTX).

Sincerely,

[Signature]

Signature applied by Lawrence R. Schiller on 08/16/2017 03:00:39 PM CDT
UNT Health Science Center
Office for the Protection of Human Subjects
Institutional Review Board
BOARD ACTION

IRB Project #: 2017-108
Date Submitted: August 29, 2017

Principal Investigator: Stephen Mathew, PhD (with CRM student: Peter Newman)

Project Title: Pain Management after Appendectomy and Cholecystectomy: An Innovative Protocol Using Exparel

Sponsor Protocol #: ____________________________

Department: Clinical Research Management / GSBS
Contact Info: x 5407

In accordance with UNT Health Science Center policy on the protection of human subjects, the following action has been taken on the above referenced project. Approval, when given, is only for the project as submitted. No changes may be implemented without first receiving IRB review and approval.

The Principal Investigator must notify the IRB immediately if any new potential Conflict of Interest arises or if CITI educational training lapses for any of the Key Personnel involved with the study.

☑ Project has received approval through: ____________________________
August 31, 2018

☐ Informed consent(s) approved as submitted on: ____________________________

You MUST use the version(s) attached rather than previously approved versions. In addition, only consent documents which bear the official UNTHSC IRB approval stamp can be used with subjects.

*Including:

☐ Study Protocol dated ____________________________ approved as submitted.

☐ Investigator’s Brochure ____________________________ approved as submitted.

☐ Protocol Synopsis approved as submitted on: ____________________________

☐ Amendment ____________________________ to the protocol approved as submitted.

☐ Progress Report/Continuing Review completed, project has received approval through: ____________________________

☐ Project has been reviewed. In order to receive approval, you must incorporate the attached modifications. You must submit one "tracked changes" version showing the markup and one "clean" copy of the revised protocol synopsis, informed consent, and advertisements to the IRB for review. YOU MAY NOT BEGIN YOUR PROJECT UNTIL NOTIFIED BY THE IRB.

☐ Project is disapproved for the reason(s) outlined (see attached).

☐ Consideration of the project has been DEFERRED pending resolution of the issues(s) outlined (see attached).

☐ Completion of project is acknowledged and all required paperwork has been received.

☑ Special Findings/Other

The UNTHSC IRB acknowledges that the activity is conducted under the oversight of the Baylor Scott and White IRB (Protocol BSWR IRB 017-245). Dr. Mathew serves as his faculty contact for this CRM internship project.

(Handwritten signature)
Chairman, Institutional Review Board

Date 9/5/17

IRB Form 2 (revised March 2011)
SPECIAL FINDINGS:

CHILDREN: The Board found the participation of children to be approvable under Subpart D of the federal regulations. Specifically, the research satisfies the requirements of:

- 45 CFR 46.404
- 21 CFR

COGNITIVELY IMPAIRED: The Board found the participation of cognitively impaired subjects to be approvable under federal regulations. Specifically, the research satisfies the requirements of:

- 45 CFR 46.111 (b)
- 21 CFR 56.111 (b)

PREGNANT WOMEN: The Board found the participation of pregnant female subjects to be approvable under Subpart B of federal regulations. Specifically, the research satisfies the requirements of: 45 CFR 46.204 (a) - (i)

FETUSES/NEONATES: The Board found the involvement of fetuses/neonates to be approvable under Subpart B of federal regulations. Specifically, the research satisfies the requirements of: 45 CFR

PRISONERS: The Board found the participation of prisoners to be approvable under Subpart C of federal regulations. Specifically, the research satisfies the requirements of: 45 CFR 46.305 (a), (b) and (c)

OTHER:

OTHER

 Expedited Review Procedures (under 45 CFR 46)

- Project ☑ Approved
- Approved for Continuation
- Modifications approved under the provisions of:
  45 CFR 46.110 (b) (1) category (5)

- 45 CFR 46.110 (b) (2) minor changes in previously approved research during the period (of one year or less) for which approval is authorized.

HIPAA Waiver: The Board finds this study meets all legal requirements for a Waiver of Individual Authorization under HIPAA pursuant to 45 CFR 164.512 (i) (2) (i)-(v) and approves the request under:

- Expedited Review Procedures (21 CFR 56.110 and 45 CFR 46.110)

Informed Consent Waiver: The Board finds this project qualifies for a Waiver of Informed Consent under the provisions of 45 CFR 46.116 (d) (1), (2), (3) & (4)

Other IRB Approved Research Documentation Includes:

Other Comments: