Table of Contents

General
- Impact of intraoperative fluid administration on outcome in patients undergoing robotic-assisted laparoscopic prostatectomy – a retrospective analysis ................................................................. 3
- The effect of adding functional classification to ASA status for predicting 30-day mortality ......................................................................................................................... 6
- Corneal abrasion in hysterectomy and prostatectomy: role of laparoscopic and robotic assistance .................................................................................................................. 8

Obstetric Anesthesia
- Neuraxial Anesthesia in Parturients with Thrombocytopenia: A Multisite Retrospective Cohort Study ........................................................................................................ 11

Pharmacology
- Tales from the Wild West of US drug pricing: the case of intravenous acetaminophen .......................................................................................................................... 14

Regional Anesthesia
- The use of Exparel (liposomal bupivacaine) to manage postoperative pain in unilateral total knee arthroplasty patients ................. 17
None of the editors or contributors have any real or potential conflicts of interest to disclose.

 Indicates Continuing Education Credit is available for this abstract and comment during the CE approval period. Continuing Education Credit is available to individual subscribers on the Anesthesia Abstracts web site at http://www.anesthesiaabstracts.com/ceMenu.php.

New health information becomes available constantly. While we strive to provide accurate information, factual and typographical errors may occur. The authors, editors, publisher, and Lifelong Learning, LLC is/are not responsible for any errors or omissions in the information presented. We endeavor to provide accurate information helpful in your clinical practice. Remember, though, that there is a lot of information out there and we are only presenting some of it here. Also, the comments of contributors represent their personal views, colored by their knowledge, understanding, experience, and judgment which may differ from yours. Their comments are written without knowing details of the clinical situation in which you may apply the information. In the end, your clinical decisions should be based upon your best judgment for each specific patient situation. We do not accept responsibility for clinical decisions or outcomes.
Impact of Intraoperative Fluid Administration on Outcome in Patients Undergoing Robotic-Assisted Laparoscopic Prostatectomy – A Retrospective Analysis

BMC Anesthesiology 2014, 14:61

Abstract

Purpose  The purpose of this study was to seek any relationship between crystalloid or colloid fluid and postoperative complications or length of hospital stay. The hypothesis was that lower volumes of intraoperative fluid administration would be associated with better clinical outcomes and a shorter hospital stay.

Background  Robot-assisted laparoscopic prostatectomy (robot prostatectomy) has rapidly become the “go-to” technique for prostatectomy, in part, because it is associated with fewer complications than open radical prostatectomy. Robot prostatectomy is performed in maximum Trendelenburg position. This extreme head-down position poses anesthetic challenges in terms of the cardiovascular, cerebrovascular, and respiratory systems. It may also result in significant swelling in the face and eyes. Each of these areas has been studied, but intraoperative fluid management during robot prostatectomy has not. In abdominal and colorectal surgery there is evidence that intraoperative fluid restriction based upon protocol or measurable goals (“goal directed”) was associated with fewer postoperative complications. Unfortunately, however, the definition of “restricted” fluids varies so widely from study to study that what was considered “restricted” fluid therapy in one study was very nearly what was considered “liberal” fluid therapy in another.

Methodology  This study was a retrospective analysis of data from 182 robot prostatectomies performed by four different surgeons at a European hospital that was just beginning to offer the robotic technique. Inclusion criterion was performance of a robot prostatectomy. Exclusion criteria were:

- blood transfusion
- history of COPD
- history of CHF
- ASA class IV

Data collected included patient demographics, intraoperative fluid administration, postoperative complications, and hospital length of stay. Fluid administration was controlled by the anesthesiologist and included crystalloids and colloids at their discretion. Colloids were either hydroxyethylstarch or modified fluid gelatin. Neither urine output nor central venous pressure were used to aid in fluid administration decisions. Urine output was unavailable due to the surgical procedure, and CVP values would have been almost meaningless in maximum Trendelenburg position. An overall analysis was performed as well as two sub-group analyses. The subgroups were patients less than 70 years old and patients 70 years to 80 years old.
Result

Demographic characteristics of the robot prostatectomy patients were as follows (values are Median followed by range, BMI = Body Mass Index kg/m², colloid fluids administered to n=143 patients):

- age 64 years (range 44-78)
- BMI 26.4 (range 19-38)
- prostate weight 42 gm (range 8-197)
- surgery length 240 min (range 135-515)
- fluids 3,600 mL (range 1,200-9,000)
  - crystalloid 3,000 mL (range 1,000-8,000)
  - colloid 500 mL (range 0-2,000)
- blood loss 400 mL (range 100-2,000)
- hospitalized 8 days (range 4-123)

Three patients had a cardiovascular complication postoperatively (1.65%). The most common urologic complication was a leak in the anastomosis between bladder and urethra in 30 patients (16.5%). Only one patient had a wound infection. Three patients (1.65%) required reoperation due to a complication.

Multiple linear regression showed no relationship between volume of crystalloid fluid received and the duration of hospitalization (P=0.7). The volume of colloid fluid received was inversely related to the duration of hospitalization; the greater the volume of colloid fluid received - the shorter the hospital stay. But this overall result was split between younger patients (~45 years old) and older patients (n=20 patients 70 years to 80 years old). Younger patients who received more colloids had shorter hospital stays while older patients who received colloids had longer hospitalizations (P=0.3).

Likewise, the association between volume of IV fluid received and the occurrence of an anastomotic leak was split between younger patients and older patients (P=0.01). Younger patients who had a greater volume of crystalloid fluid had a lower incidence of anastomotic leak. Patients older than 70 years who had a greater volume of crystalloid fluid had a higher incidence of an anastomotic complication (primarily leaking). No other complications were associated with the volume of fluid received.

Conclusion

Higher volumes of crystalloid fluids received were associated with anastomotic leakage in patients more than 70 years old. Higher volumes of colloid administration were associated with longer hospital stays in patients more than 70 years old. The opposite was true of patients around 45 years old.

Comment

I have a special interest in these cases and I’ve done a lot of them. This study used data that truly was during the surgeon’s learning curve. My surgeon was experienced and the operative time was normally less than 90 minutes. Over two hours was a long one. Once the surgeons get used to doing the case with a robot, blood loss is almost always less than 125 mL. In this retrospective study the median case duration was 4 hours (max. 8.5 hours) and median blood loss was 400 mL (max. 2,000 mL). So, my first observation is that once the surgeons get good at the technique, there are some anesthetic challenges - a big pneumoperitoneum and maximum Trendelenburg position - but how much fluid to give during the case shouldn’t usually be one of them.

In my opinion, this study is fairly week in a number of areas. Not only was it retrospective, so there is a lot we
don’t know - a lot that wasn’t controlled for, but the magnitude of the variability in the measures of interest was enormous. Surgery duration was from 2¼ hours to 8½ hours. Crystalloid administration was from 1 L to 8 L. Colloid IV fluid administration was up to 2 L. Blood loss was from 100 mL to 2,000 mL; wow. And, one of the many things we don’t know was how fluid administration correlated with the length of the case and the volume of blood loss. Given all this, I think we need to be careful how much we try to take away from this study.

So what am I willing to believe from this study?

1) Not surprisingly, patients in the “younger” age range (45 years old to less than 70 years old) who were presumably healthier than those over 70 years old, did just fine almost no matter how much fluid they received. This really isn’t news.

2) There did appear to be an association between age over 70 years, larger volumes of fluid administration, and both a longer hospital stay and more frequent anastomotic complications. The problem is we can’t define how much fluid is too much because there is no agreement on what “fluid restriction” and “liberal fluid administration” is yet.

There is beginning to be scientific evidence that restricting fluids during general anesthesia reduces complications under some circumstances. From what I’ve read so far I think three categories will emerge. Healthy patients having short procedures will benefit from liberal fluid administration. In longer cases, say 2-3 hours, we will probably develop fluid administration protocols designed to minimize fluid administration, and this will result in an improved postoperative course. In longer cases and sicker patients, fluids will need to be administered based upon specific hemodynamic goals (“goal-directed therapy”). This last category will require especially careful monitoring, often invasive monitoring, upon which to base the decision to administer fluids.

Michael A. Fiedler, PhD, CRNA

Other robot prostatectomy studies appearing in Anesthesia Abstracts include:


The effect of adding functional classification to ASA status for predicting 30-day mortality

Anesth Analg 2015;121:110-116

Abstract

Purpose  Anesthesia providers use the American Society of Anesthesiologists (ASA) physical status classification when performing a preanesthetic assessment. This study looked at whether functional capacity was an independent predictor of 30-day and long-term postoperative mortality. If it is an independent predictor, how could it be incorporated into the ASA classification to make it more meaningful?

Background  The ASA physical status classification, modified in 1961, is a physical status assessment that has been around since 1941. It has been validated as one of the most reliable predictors of postoperative mortality. There are some limitations in risk stratification in certain patient populations due to patients having several comorbid conditions. These patients are limited to classification as ASA III and IV. It has been noted that an independent predictor of 30-day and long-term mortality includes functional capacity to perform activities of daily living. However, functional ability is not considered when assigning the ASA physical status classification.

Methodology  Charts from 12,324 patients undergoing noncardiac surgery between 1998 and 2010 were reviewed in this retrospective cohort study. The primary outcome variable was long-term mortality and death within 30 days. Postoperative complication was the secondary outcome variable.

The Veterans Affairs Surgical Quality Improvement Program (VASQIP) database was populated with patient information such as ASA class, comorbidities, and functional status. Each patient’s ASA status was coded to include an “A” for functionally independent or a “B” for partial or full functional dependence. Comparison of the ASA classes and subclasses with their bordering counterparts then occurred. Data analysis included ASA class, functional status, clinical and demographic characteristics, preoperative labs, anesthesia type, procedure, length of stay, and perioperative morbidity and mortality. Mortality was documented in a 2013 follow up.

Descriptive statistics were used for demographics and morbidities. The traditional and modified ASA classifications in predicting long-term survival and death within 30 days were plotted. The predictive value of each model was then calculated by the area under the curve. Significant variables from a univariate log-rank model, excluding ASA classifications, were included in a multivariate logistic regression to evaluate their ability to predict mortality.

Result  Of 12,324 surgical patients
I. 381 (3%) were ASA I
II. 3,705 (30%) were ASA II
III. 6,513 (53%) were ASA III
IV. 1,632 (13%) were ASA IV
V. 93 (0.8%) were ASA V

Males made up the majority of the patients (95%). The group lacking functional capacity to perform
activities of daily living (group B) had more comorbidities. Postoperative complications, which included:

- 30-day mortality
- myocardial infarction
- cardiac arrest
- postoperative pneumonia
- urinary tract infection
- wound dehiscence
- renal insufficiency
- returning to the OR for reoperation
- hospital length of stay

were all significantly more likely in the group without the functional capacity to perform activities of daily living (group B).

Within each ASA class, the odds ratio for mortality was significantly greater in patients who lacked the functional capacity to perform activities of daily living (group B). This group also had a significantly greater mortality than functionally independent patients (group A) in the next highest, sicker, ASA class. When a modified ASA classification was used which included an assessment of the ability to perform activities of daily living, predicting death within 30 days postop was improved almost 5%. Patients with limited functional capacity to perform activities of daily living (group B) and emergency surgery were significant predictors of postoperative mortality. Patients lacking the functional capacity to perform activities of daily living were almost 5 times more likely to die within 30 days of surgery. Emergency surgery increased the risk of mortality 2.5 times.

**Conclusion**

Lacking the functional capacity to perform activities of daily living was an independent predictor of mortality within each ASA physical status class. Within a given ASA class, patients who lacked the functional capacity to perform activities of daily living had a greater risk for mortality than functionally independent patients in the next higher ASA class. The concept of functional independence vs. the lack of functional capacity to perform activities of daily living could be used as a basis for refining the ASA physical status classification.

**Comment**

This article was very intriguing to me. I found the information useful. Although changes have not been made to the ASA physical status classifications, this information can make us more aware of potential issues with patients who have limitations in their ability to perform activities of daily living. This is useful information to add an additional layer to any assessment. Although changes have not been made to the classifications, it would be simple to add a check box to an assessment that would indicate full ability or limitations on the ability to perform activities of daily living. In our facility, it would take very little additional time with the assessment since a physical assessment is completed for every patient. With the information in this study, anesthetists would be more aware of the increased risk in patients who have limited ability to perform activities of daily living even in a lower ASA classification and have their assessment reflect it.

**Heather Fields, MBA, MSN, CRNA**
Corneal abrasion in hysterectomy and prostatectomy: role of laparoscopic and robotic assistance

Anesthesiology 2015;122:994-1001
Sampat A, Parakati I, Kunnavakkam R, Glick DB, Lee NK, Tenney M, Eggener S, Roth S

Abstract
Purpose The purpose of this study was to describe the incidence and differences in corneal abrasion between robotic-assisted laparoscopic surgery vs. open procedures for prostatectomy and hysterectomy.

Background The use of minimally invasive surgical techniques (laparoscopic with or without robotic assistance) for hysterectomy and robotic-assisted laparoscopic prostatectomy have increased over the last decade. Robotic-assisted laparoscopic prostatectomy and hysterectomy are performed in steep Trendelenburg position. Some small case series suggest these procedures are associated with increased risk of corneal abrasion, secondary to increased intraocular pressure with corneal and conjunctival edema. This study hypothesized that robotic-assisted laparoscopic and simple laparoscopic techniques are associated with increased risk of corneal abrasion.

Methodology Investigators extracted data from between 2000 and 2011 from the National Inpatient Sample discharge records on outcomes in patients who underwent open or robotic-assisted laparoscopic radical prostatectomy and open, laparoscopic, or robotic-assisted laparoscopic hysterectomy using ICD-9 CM codes. The presence or absence of corneal abrasion was recorded for each patient. Investigators examined the rate of corneal abrasion over time for the different surgical techniques for prostatectomy and hysterectomy. Descriptive and inferential statistics were used. A P < 0.05 was significant.

Result There were 166,942 radical prostatectomies with 295 corneal abrasions from 2000 to 2011 (1.8 per 1,000). The rate increased three-fold from <10 patients with corneal abrasion in 2000 (0.8 per 1,000) to 46 patients in 2011 (2.8 per 1,000).

There were 216,890 laparoscopic hysterectomies with 275 recorded corneal abrasions from 2000 to 2011 (1.3 per 1,000). In 2000 there were <10 corneal abrasions (0.9 per 1,000) and in 2011 there were 55 (2.1 per 1,000). In contrast, the rate of corneal abrasion reported during open hysterectomy was stable from 2000 to 2011, with a reported rate of 0.3 per 1,000 patients (Figure 1).

Discharge records in October 2008 started including an ICD-9 code for robotic-assistance (Figure 2). Univariate analysis demonstrated a significantly higher rate of corneal abrasion from 2009-2011 for robotic-assisted prostatectomy compared to open procedures (OR = 1.55, 95% CI, 1.01-2.36). African Americans had a reduced risk of corneal abrasion (OR = 0.062, 95% CI, 0.009-0.446).
Analysis of hysterectomy discharge records from 2009-2011 demonstrated that patients undergoing robotic-assisted laparoscopic hysterectomy had a 7.7 times greater odds of experiencing a corneal abrasion compared to open procedures (OR = 7.78). A lower but still significantly increased rate of corneal abrasion was seen when comparing simple laparoscopic hysterectomy (no robot) to open procedures (OR = 3.69). Older age (OR = 1.02) and increased number of chronic medical conditions (OR = 1.14) were identified as risk factors for corneal abrasion after hysterectomy. African American race was associated with a lower risk of corneal abrasion (OR = 0.27).
Conclusion  Laparoscopic-assisted and robotic-assisted hysterectomy increased the odds of corneal abrasion 4 to 7 times compared to open procedures.

Comment
Robotic procedures are some of the most challenging procedures to perform. They require steep trendelenburg positioning for extended periods of time. This results in increased intraocular pressure and secondary corneal edema and increases the risk, as we saw in this study, for corneal abrasion after hysterectomy. For hysterectomy, both robotic-assistance and laparoscopic techniques alone increased the risk of corneal abrasion. However, the authors did not comment in their conclusion on robotic-assisted prostatectomy and whether or not this technique increased the risk of corneal abrasion.

Their univariate analysis suggested it does increase the risk compared to open procedures (OR = 1.5), but when they controlled for race the P value was not significant.

This does NOT mean corneal abrasion is not a risk associated with robotic-assisted prostatectomy. Rather, I suspect this is the case of a Type II error, meaning the authors say there is no difference when in fact there is. The study was probably underpowered to examine this outcome after robotic prostatectomy. If you look at Figure 1, you see a clear trend of increased corneal abrasion starting in 2006; although, the authors did not have data on what type of prostatectomy was performed during that time period; laparoscopic or open. This increasing trend correlates with the introduction of robotic techniques in 2009.

So I would still consider corneal abrasion a potential complication that can occur after robotic-assisted prostatectomy.

So what can we do to prevent corneal abrasions?
Protect the eyes. If you have disposable eye guards, use them. Be gentle when taping the eyes, making sure to keep the eyelid closed. Be gentle when removing tape and cognizant of patients or equipment accidentally scratching their eyes. Finally, talk with your surgeons about how much steep trendelenburg they really need. See if they can get away with a less steep angle. Also remember to tell patients corneal abrasion is a potential complication during the consent process.

Dennis Spence, PhD, CRNA

Editor’s Note: We saw higher rates of corneal abrasions in our robotic prostatectomy patients as well. I agree with Dr. Spence and each of his recommendations for reducing the risk of corneal abrasion in these patients. I’d like to add that since corneal edema may be involved and won’t go away when you wake the patient up, PACU personnel need to be educated about the increased risk of corneal abrasion as well. We don’t know when the corneal injury is occurring. Michael A. Fiedler, PhD, CRNA

The views expressed in this article are those of the author and do not reflect official policy or position of the Department of the Navy, the Department of Defense, the Uniformed Services University of the Health Sciences, or the United States Government.
Obstetric Anesthesia

**Neuraxial Anesthesia In Parturients With Thrombocytopenia: A Multisite Retrospective Cohort Study**

Anesth Analg 2015;121:988–91
Goodier CG, Lu JT, Hebbar L, Segal BS, Goetzl L

**Abstract**

**Purpose** The purpose of this study was to improve the estimate of the risk of an epidural hematoma following neuraxial anesthesia / analgesia in parturients with platelet counts below 100,000 mm$^3$.

**Background** During pregnancy, platelet counts below 150,000 mm$^3$ occur in 7% to 10% of parturients. Thrombocytopenia increases the risk of an epidural hematoma when neuraxial anesthesia or analgesia is used. Historically, platelet counts below 100,000 mm$^3$ have been considered a strong contraindication to performing a spinal or epidural. Nevertheless, many case reports have described the use of neuraxial techniques in parturients with platelet counts well below 100,000 mm$^3$. An agreed upon threshold below which neuraxial techniques should not be used in parturients does not exist. To further complicate this risk-benefit decision, omitting neuraxial analgesia in a parturient often means they will experience considerable pain. Other methods of pain relief are often quite inferior. If a patient ultimately goes for a cesarean section, a previous decision against neuraxial anesthesia for fear of the risk of an epidural hematoma means they will receive a general anesthetic for surgery. In parturients, general anesthesia is known to be associated with significant risks of morbidity and mortality, especially related to airway management.

**Methodology** This study was a retrospective record review from two geographically distant clinical sites in the USA. Inclusion criteria was simply admission for delivery with a platelet count below 100,000 mm$^3$ over a 15-year period. In addition to collecting demographic variables and platelet counts, the diagnosis for low platelet counts was collected. At one institution the Arrow Flextip catheter was used for epidurals. The other institution used the Braun Perifix epidural catheter.

**Result** Over the 15-year study period 280 patients had a platelet count below 100,000 mm$^3$; this represented 0.54% of parturients cared for at the two hospital systems. In these 280 parturients with low platelet counts:

- 36% received an epidural or spinal-epidural
- 25% received a spinal
- 38% received neither

No cases of epidural hematoma occurred. This data was combined with data from 326 cases in previous studies for a total of 499 parturients upon which to base statistical calculations. The maximum rate of epidural hematoma was calculated from these 499 women who did not develop an epidural hematoma by assuming that the very next case, the 500th parturient,
would develop this complication. [Editor’s Note: this “maximum rate” was represented by the upper end of a 95% Confidence Interval for the true rate of epidural hematoma based upon the assumption that 1 in 500 parturients developed the complication. See comment section for more information.] Based upon this small data set, the upper limit of the risk of an epidural hematoma in parturients with platelet counts below 100,000 mm$^3$ who received a spinal or epidural was calculated to be 0.6%.

As expected, platelet counts only slightly lower than 100,000 mm$^3$ were seen more commonly than platelet counts far below 100,000 mm$^3$. (The lowest platelet count in any of the records reviewed was 28,000 mm$^3$.) Due to this fact, the lower the platelet count of interest, the less data there was upon which to base an estimate of risk for epidural hematoma if neuraxial anesthesia were used. Due to this fact, there was not enough data upon which to project the risk of epidural hematoma following neuraxial anesthesia in parturients with platelet counts below about 80,000 mm$^3$.

**Conclusion** Combining the data from this retrospective study with other published data, the worst-case scenario (the upper limit of a 95% Confidence Interval) for the risk of epidural hematoma in parturients with a platelet count below 100,000 mm$^3$ who received neuraxial anesthesia was calculated to be 0.6%. Insufficient data existed to characterize the risk of epidural hematoma following neuraxial anesthesia in parturients with platelet counts below 80,000 mm$^3$.

**Comment**

The “normal range” for platelet count in a term pregnant woman is higher than in a non-pregnant individual, with a low end of about 150,000 mm$^3$. This study tackles a difficult problem, trying to figure out the risk of a parturient developing an epidural hematoma when their platelet count is low (less than 100,000 mm$^3$) and they’ve had a spinal or epidural. An epidural hematoma is a rare complication and very large numbers of patients are needed to study rare events.

In an attempt to get around the need for very large numbers of patients, the investigators combined two techniques. The first technique was simply the assumption that whatever number of patients had neuraxial anesthesia without an epidural hematoma, the very next patient would experience the complication. The second assumption was what I’m calling the “worst-case scenario” calculation. In other words, if the very next patient had an epidural hematoma what risk of epidural hematoma would that calculate out to? It is not, as you might expect 1/500, or 0.2%. Statistically, when we only have a sample, especially a small sample and especially when the sample isn’t random, the numbers we come up with are what I like to call “fuzzy;” we can’t know them with certainty. But we can calculate a range for numbers like the risk of an epidural hematoma in parturients who have had neuraxial anesthesia. One of our favorite ranges is the Confidence Interval (CI). A 95% CI says “we are 95% sure the real number lies between the low end and the high end of the Confidence Interval.” So, the “worst-case scenario” is the high end of the 95% Confidence Interval.
Interval. That is what the investigators used here to produce the risk of an epidural hematoma following neuraxial anesthesia in parturients with a platelet count lower than 100,000 mm$^3$. Their risk of 0.6% is certainly not definitive; I’d call it a “best estimate” given the available data.

I commend the investigators for their ingenuity. I believe they have added to our understanding of the risk of epidural hematoma following, say, labor epidural analgesia. But we must be cautious about putting too much faith in their results. If you flip a coin 10 times the most common outcome is that you’ll get heads 5 times and tails 5 times. But, rarely, you can flip a coin 10 times and get heads 0 times, other times you get heads only once, and other times just 2 times, etc. This study had only 499 patients and was looking for a rare event but none of the patients had the complication. So even assuming the very next patient would have an epidural hematoma may have underestimated the real incidence of the complication just like flipping a coin 10 times and getting only 2 heads underestimates the probability of getting heads.

So can we know anything for sure after reading this study? I take away three things.

1) The most obvious is that the further the platelet count goes below 100,000 mm$^3$, the higher the risk of an epidural hematoma.

2) It provides some reassurance that parturients with stable platelet counts between 80,000 mm$^3$ and 100,000 mm$^3$ may be at only marginally higher risk of an epidural hematoma than women with a platelet count above 100,000 mm$^3$. (Note that platelet counts are often not stable in women with preeclampsia.) And, the increased risk may be balanced out by the risks of general anesthesia if they are having a Cesarean section.

3) The risk of an epidural hematoma is lower following a spinal than following an epidural. So an easily placed spinal for a C-section in a woman with a stable platelet count of 85,000 mm$^3$ looks a little better than it used to when compared to the risks of general anesthesia.

Michael A. Fiedler, PhD, CRNA
Pharmacology

Tales from the Wild West of US Drug Pricing: The Case of Intravenous Acetaminophen

Poeran J, Babby J, Rasul R, Mazmumdar M, Memtsoudis SG, Reich DL

Abstract

Purpose The purpose of this study was to describe the overall use and costs associated with the administration of intravenous acetaminophen in the United States.

Background Intravenous acetaminophen (Ofirmev, Mallinckrodt Pharmaceuticals) is approved by the FDA for the management of mild to moderate pain, moderate to severe pain with adjunctive opioid analgesics, and for the reduction of fever. Intravenous acetaminophen reaches a rapid maximum plasma level 30 minutes faster and achieves a 70% higher maximum concentration compared to oral acetaminophen. Significant pain relief starts 15 minutes after administration of a 1,000 mg infusion. The maximum total daily dose is 4,000 mg/day (650 mg every 4 hours or 1,000 mg every 6 hours) in adults and max 75 mg/kg a day in children aged 2 years to 13 years (<50 kg). It should be given cautiously in patients with liver or kidney impairment.

Only 15 weeks after becoming available, Ofirmev was on formulary in 675 hospitals across the USA. Ofirmev was originally marketed by Cadence Pharmaceuticals but was later acquired by Mallinckrodt Pharmaceuticals in 2014. The initial wholesale acquisition cost per vial was $12.43 (January 2013), but after Mallinckrodt Pharmaceuticals acquired the drug the price increased to $35.40 per vial.

Numerous studies have demonstrated the efficacy of intravenous acetaminophen as an adjunct to multimodal analgesia, but the dramatic increase in price per vial has led many facilities to question cost-to-benefit relationship of intravenous acetaminophen. Furthermore, there are no large-scale data available on the current utilization of intravenous acetaminophen in the USA.

Methodology This was a retrospective study of intravenous acetaminophen utilization in the USA. Investigators queried the national claims-based Premier Perspective database for data on the following surgeries:

- major orthopedic (knee/hip/spine)
- cardiothoracic (CABG)
- gynecological (hysterectomy)
- general (open colectomy)

The Premier database only includes data from 20% of U.S. hospitals. Data was recorded on patient and hospital variables and on the use and overall costs of IV acetaminophen. Investigators estimated the expected cost increase by using the 2013 overall use of acetaminophen vials and the hospital that used the maximum number of vials in 2013. The following formula was applied: number of vials x (new...
The use of intravenous acetaminophen increased between 23% and 32% since 2011 (Figure 1). Intravenous acetaminophen was more frequently used in large (>500 beds), urban, academic medical centers than smaller, rural hospitals, and non-academic medical centers. Demographic variables did not explain differences in use of intravenous acetaminophen. Major orthopedic surgeries had the highest absolute use of intravenous acetaminophen, with 125,301 vials used in 2013. This was associated with a $2.78 million dollar increase in overall cost since the price increase with a total cost at $35.40 per vial or $4.43 million (Table 1). The estimated costs of intravenous acetaminophen at the hospital with the greatest reported use in 2013 ranged from $61,171 (CABG surgery) to $246,667 (major orthopedic surgery).

**Table 1. Use of Intravenous Acetaminophen in USA - 2011-2013**

<table>
<thead>
<tr>
<th>Surgery</th>
<th>2013 Total Vials Used</th>
<th>Estimated Cost Increase</th>
<th>Estimated Average Increase per Hospital</th>
<th>2013 Max Vials Used at a Hospital</th>
<th>Estimated Cost Increase*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colectomy</td>
<td>34,000</td>
<td>$780K</td>
<td>$5,556</td>
<td>1,746</td>
<td>$40,106</td>
</tr>
<tr>
<td>Hysterectomy</td>
<td>35,376</td>
<td>$812K</td>
<td>$5,216</td>
<td>1,907</td>
<td>$43,804</td>
</tr>
<tr>
<td>Major Ortho</td>
<td>125,301</td>
<td>$2.87 million</td>
<td>$13,951</td>
<td>6,968</td>
<td>$160,055</td>
</tr>
<tr>
<td>CABG</td>
<td>20,354</td>
<td>$467K</td>
<td>$7,121</td>
<td>1,728</td>
<td>$39,692</td>
</tr>
</tbody>
</table>

Notes: * $22.97 per vial increase

Notes: $35.40 per vial
Conclusion  The data demonstrated a substantial increase in the overall costs for intravenous acetaminophen administration for select major surgeries.

Comment  I remember when intravenous acetaminophen came to my hospital. Many providers (including myself) were administering it like candy on Halloween; it seemed like every patient was getting it! The drug representatives brought us coffee and donuts and did a good job of describing the pharmacokinetics and benefits of intravenous acetaminophen over oral administration. I agree, the data was pretty compelling, and it seemed to fit nicely as an adjunct to multimodal analgesia. Then the price increased almost 2.8 fold, from a wholesale price of $12.43 to $35.40 literally overnight. This caused many hospital administrators to take a deep breath and really question widespread use of the drug. Our pharmacists removed the Ofirmev vials from our anesthesia workstations in the operating room, making it harder for us to readily administer it. I imagine this also occurred in many other institutions where our readers work.

With skyrocketing health care costs, I think it is important that we as anesthesia providers practice cost-conscious, evidence-based practice. We should base our decisions on evidence and what is best for our patients but should keep in mind costs and, whenever appropriate, consider cheaper alternatives if the same outcomes are achieved. Whether or not this includes intravenous acetaminophen should be based on a case-by-case basis, rather than giving or ordering it on all patients.

Dennis Spence, PhD, CRNA

The views expressed in this article are those of the author and do not reflect official policy or position of the Department of the Navy, the Department of Defense, the Uniformed Services University of the Health Sciences, or the United States Government.
The use of Exparel (liposomal bupivacaine) to manage postoperative pain in unilateral total knee arthroplasty patients

J Arthroplasty 2015;30:325-9
Surdam JW, Licini DJ, Baynes NT, Arce BR

Abstract

Purpose The purpose of this study was to determine if a periarticular block with Exparel (liposomal bupivacaine) provided similar pain control and functional outcomes to a conventional single shot femoral nerve block after Total Knee Arthroplasty (TKA).

Background Total Knee Arthroplasty is associated with significant postoperative pain. Uncontrolled postoperative pain can interfere with physical therapy participation and recovery. Femoral nerve blocks (FNBs) provide excellent postoperative pain relief after TKA but not without disadvantages. FNBs can cause quadriceps weakness and impair a patient’s ability to ambulate and may lead to falls. This may, in turn, delay recovery and result in a longer hospital stay. As a result, many orthopedic surgeons have begun using periarticular injections of a combination of local anesthetic with various adjuncts (e.g., epinephrine, ketorolac, morphine) as an alternative to FNBs. However, the duration of action of a periarticular block is typically less than 16 hours. Studies suggest they decrease pain and improve functional outcomes, such as the distance walked, but differences in research methods from study to study make it difficult to compare results.

Liposomal bupivacaine (Exparel) is a long-acting local anesthetic which is FDA approved for administration into the surgical site to produce postsurgical analgesia. Exparel Liposomal bupivacaine is released over 72 hours using Depofoam® as a delivery platform. Clinical trials in hemorrhoidectomy and bunionectomy patients demonstrated that Exparel significantly decreased pain intensity during the first 24 hours but was no different than placebo between 24 and 72 hours. However, opioid consumption was decreased. Because of its long duration of action and promising findings from retrospective studies, many orthopedic surgeons have begun using Exparel in their periarticular injections during TKA. However, no randomized controlled trials have been conducted comparing it to traditional FNBs for postoperative pain control or its effects on physical therapy after TKA. The investigators hypothesized that liposomal bupivacaine would provide similar analgesia and result in similar function compared to FNBs after Total Knee Arthroplasty.

Methodology This was a prospective, randomized controlled trial. Patients received either a periarticular block with Exparel or a single shot FNB for postoperative pain control after TKA. The primary outcome was differences in pain control during the first three days after TKA; defined as the
average pain scores during the admission. The secondary outcomes included differences in:

- total morphine equivalents (opioid consumption)
- postoperative nausea and vomiting
- distance ambulated
- ability to ambulate on the first postoperative day
- degree of flexion and extension of operative knee
- ability to perform a straight leg raise
- hospital length of stay

Pain scores were documented every 4 hours and all medications administered were transcribed from the medical record. All surgeries were performed by a single surgeon. All patients received a single shot spinal with 0.75% bupivacaine for the surgery, oxycontin SR 10 mg BID x2 doses, then hydrocodone q4 hours, oxycodone prn, celoxib BID, metoclopramide, and ondansetron prn.

Patients in the FNB group received a preoperative single shot ultrasound-guided femoral nerve block with 40 mL of 0.5% ropivacaine with 1:200,000 epinephrine, plus 30 mg of 1% tetracaine. Patients in the Exparel group received an intraoperative periarticular injection of 266 mg of Exparel diluted in 60 mL. Periarticular injections were made using an 18 g needle as follows:

- 5 mL in each medial and lateral posterior capsule
- 5 mL into the medial femoral periosteum
- 10 mL in medial meniscal remnant and inferior medial capsule
- 10 mL in superomedial capsule and vastus medialis fascia
- 10 mL in superolateral capsule, vastus lateralis fascia, and lateral meniscus remnant
- 15 mL into both the medial and lateral subcuticular tissues just beneath the skin

A t-test was used to compare results. A P value < 0.05 was reported as significant. [Contributing Editor’s note: a more appropriate statistical analysis would have been a repeated measures analysis of variance with adjustment of the P value for multiple comparisons. Also an equivalence or noninferiority design and analysis plan should have been used.]

**Result**

Eighty patients, 40 in each group, completed the study. No significant differences were seen in baseline demographics. Mean pain scores were similar in the FNB and Exparel groups (2.9 vs. 3.4, P = NS). Patients in the FNB group had significantly lower pain scores on POD 0 (2.9 vs. 3.8, P < 0.05). Thereafter, pain scores were similar (Figure 1). No differences were seen in average opioid consumption over the three postoperative days (POD) between the groups; 29 mg vs. 31 mg. Patients in the Exparel group had significantly higher opioid requirements on POD 0 compared to the FNB group (26 mg vs. 14 mg, P < 0.05; Figure 1). However, on POD 1 the FNB group required significantly more opioids than the Exparel group (9 mg vs. 4 mg, P < 0.05). Thereafter, opioid consumption was similar, although the FNB group did have higher opioid requirements the remaining two days (6 mg vs. 1.5 mg). PONV rates were similar.

Physical therapy functional outcomes demonstrated that the FNB group had similar flexion and extension each day. But patients in the Exparel group could ambulate a longer distance than the FNB group on POD 1 (152 feet vs. 108 feet, P < 0.05). Only 10% of patients in the FNB group could ambulate on POD 0 (P < 0.05), and only 17% of patients in the FNB group could perform a straight leg bend on POD 0.
compared to 100% of the Exparel Group for both outcomes (Table 1). Mean hospital length of stay was significantly shorter in the Exparel group (2.4 days vs. 2.7 days, P = 0.03.) One patient fell in the FNB group.

**Conclusion**  Pain control with the Exparel periarticular block was at least as good as a FNB after Total Knee Arthroplasty. Exparel was associated with earlier ambulation, longer walking distances, and earlier discharge.

**Comment**  TKA is one of the most painful surgeries. Multimodal analgesic regimens are the mainstay of postoperative pain control after TKA. Traditionally, FNB blocks, either as a single shot or continuous infusion have been used in multimodal pain plans. Unfortunately, FNBs may delay ambulation and prolong discharge due to quadriceps weakness. However, ineffective pain control can do the same thing; so it is a double-edged sword. What I have seen in my clinical practice is the pendulum is swinging away from more effective pain control with an FNB to possibly less effective pain control with periarticular injections of various local anesthetic cocktails, which may lead to earlier discharge.

At my institution we have transitioned away from a continuous FNB catheter after TKA to periarticular injection of bupivacaine mixed with ketorolac and epinephrine. We have not started using Exparel in our periarticular injections, mainly because our surgeons want to see more data on its efficacy. This study, while having some weaknesses, does provide evidence that Exparel may provide good pain control without impairing recovery after TKA.

---

**Figure 1. Pain Scores and Opioid Use**

<table>
<thead>
<tr>
<th>POD 0</th>
<th>POD 1</th>
<th>POD 2</th>
<th>POD 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain Scores 0 - 10</td>
<td>Pain Scores FNB</td>
<td>Pain Scores Exparel</td>
<td>Morphine Equivalents (mg)</td>
</tr>
<tr>
<td>Pain Scores FNB</td>
<td>Pain Scores Exparel</td>
<td>Opioids FNB</td>
<td>Opioids Exparel</td>
</tr>
</tbody>
</table>

**Note:** FNB = Femoral Nerve Block. POD = Postoperative Day. Solid lines are for pain scores. The dotted lines are for total morphine equivalents. Pain scores and opioid consumption higher in Exparel group on POD 0 (P < 0.05). Opioid consumption higher in FNB group on POD 1 (P < 0.05).
Finally, your surgeons need good injection techniques, dilute one vial of Exparel in 90 mL of saline. Volume dilute the local in a larger volume; I have seen some leaking of the local from the site of injection. is injected at. If you use an 18 gauge needle there may have influenced the results. Exparel works at the site it weakness. The other tip is the surgeon needs to use a nice technique because it minimizes quadriceps injections, but I recommend readers investigate this

There are a few caveats. First, if your surgeons are going to use Exparel, then you need to bridge the gap during that first 24 hours because of the slow release of bupivacaine. I have heard some surgeons mixing plain bupivacaine with Exparel in their periarticular injections, but I recommend readers investigate this themselves. Some anesthesia providers are performing a single shot or continuous adductor canal block. This is a nice technique because it minimizes quadriceps weakness. The other tip is the surgeon needs to use a small gauge needle to inject; nothing bigger than a 21 gauge. In this study they used an 18 gauge. This could have influenced the results. Exparel works at the site it is injected at. If you use an 18 gauge needle there may be some leaking of the local from the site of injection. Dilute the local in a larger volume; I have seen some dilute one vial of Exparel in 90 mL of saline. Volume compensates for surgeon poor injection technique.

Finally, your surgeons need good injection techniques, and they need to make sure they inject into the posterior knee capsule since posterior knee pain is common after TKA. But they need to be cautious in blindly injecting back there because the popliteal artery and vein are right there!

**Mean length of stay significantly shorter in Exparel group 2.36 ± 0.71 vs. 2.65 ± 0.48, P = 0.03.**  
*P < 0.05.

Dennis Spence, PhD, CRNA

The views expressed in this article are those of the author and do not reflect official policy or position of the Department of the Navy, the Department of Defense, the Uniformed Services University of the Health Sciences, or the United States Government.