Comparison of Bilateral Transversus Abdominis Plane Block with Exparel versus Continuous Epidural Analgesia With Bupivacaine:

A Randomized, Controlled Trial

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Specific Aims

Pain management after major abdominal surgery remains challenging. The best-accepted analgesic approach is continuous epidural analgesia, however, epidural analgesia can cause hemodynamic instability, along with motor weakness and consequent restriction of ambulation. Furthermore, epidural catheter placement can be time consuming and challenging, and is contraindicated in anti-coagulated patients.

The Transversus Abdominis Plane infiltration is an alternative approach to providing postoperative analgesia to the anterior abdominal wall. TAP infiltration are relatively easy to perform, generally safe, and can be performed in patients who are anti-coagulated. TAP infiltration can be performed as a single injection, or a catheter can be inserted for continuous local anesthetic infusion. Single-shot TAP infiltration with conventional local anesthetics do not last sufficiently long to provide effective postoperative analgesia. However, recently developed liposomal bupivacaine provides much longer-lasting analgesia than plain bupivacaine.

Therefore we proposed to compare single-shot TAP infiltration with liposomal bupivacaine were as effective as continuous epidural analgesia. The proposed research will have the following specific aims, all of which will be assessed over 72 hours, or the duration of hospitalization if shorter:

Primary Aim: Bilateral TAP blocks with single-shot liposomal bupivacaine are noninferior to continuous epidural analgesia with conventional bupivacaine for both pain control and opioid consumption.

Secondary Aim 1: To compare the effect of TAP block with Exparel and epidural analgesia on activity after surgery.

Secondary Aim 2: To compare TAP block with Exparel and epidural analgesia on opioid related side effect.

Secondary Aim 3: To assess hemodynamic changes with TAP block with Exparel and epidural analgesia.

Secondary Aim 4: To compare quality of recovery after anesthesia with TAP block Exparel and epidural analgesia.

Secondary Aim 5. To compare length of stay in TAP block with Exparel and epidural analgesia patients after surgery.

Secondary Aim 6. To evaluate cost-effectiveness of TAP block with Exparel.

1. Background

A. Postoperative pain

Pain is a psychological sensory experience that is provoked by surgical tissue injury. Postoperative pain results from a of combination of nociceptive and inflammatory components.[1] The nociceptive component results from activation of peripheral sensory neurons damaged by surgical incision and fades gradually as tissues heal. The inflammatory component enhances pain sensitivity via release of mediators from the surgically injured tissue. Central neuronal sensitization also seems to contribute to postoperative pain and hyperalgesia.[1,2] Both mechanisms contribute to resting pain is in and around surgical incisions. Movement of wounds or touching them, breathing, coughing, and gastrointestinal motility can all evoke pain.

Unrelieved postoperative pain leads to multiple physiological and psychological consequences, which potentially worsen outcomes. For example, inadequate perioperative analgesia is associated with myocardial ischemia, impaired wound healing, delayed gastrointestinal motility, atelectasis, and postoperative pneumonia.[3-5] Furthermore, poorly controlled acute pain is strongly associated with development of persistent incisional pain, which can be devastating for patients.[6,7]

B. Postoperative pain management and Regional Analgesia

Postoperative pain management has improved, but remains problematic. Thirty percent of patients still report severe postoperative pain, and 47% report moderate pain.[8] Researchers estimate that only one in four surgical patients in the USA receive adequate relief of acute pain. Consequently, postoperative pain remains the major preoperative concern for patients having surgery.[9]

Pain involves multiple mechanisms and is thus ideally treated with a variety of analgesic techniques with additive, or better, synergistic effects.[1] In theory, at least,

combining techniques improves overall analgesia while reducing side effects. Consistent with this theory, studies indicate that multimodal analgesia shortens hospitalization times, improves recovery and function, and decreases health care costs.[1,10]

Multimodal analgesia can be achieved by combining various classes of drugs.[1,10,11] But the most common approaches are a combination of an opioid and non-opioid, with or without regional anesthesia-analgesia.[11] While opioids remain the mainstay for treatment of postoperative pain, sole reliance on opioids is often inadequate and lead to substantial side effects including ileus, sedation, respiration depression, and hyperalgesia.[12] There is also evidence opioids impair cellular and humoral immune function in humans, thereby potentially enhancing infection risk.[13-16] An important clinical goal is thus to decrease opioid use and, consequently, reduce opioid-related side effects.

Regional anesthesia (RA) is a promising approach to reducing the need for high-dose opioids. Regional techniques can be categorized as neuraxial blocks (spinals, epidural) that involve local anesthetics injected around the spinal cord or as peripheral nerve blocks that involve local anesthetic administration near peripheral nerves. The basis of regional analgesia is local anesthetics or/and opioids which locally block voltage-gated sodium channels, thus interrupting nerve conductions and rendering enervated regions insensitive to pain.[17] Peripheral nerve blocks, especially, have become popular in recent decades largely because improvements in ultrasound technology make blocks faster and safer — and because blocks speed recovery and improved patient satisfaction.[18]

Surgery is associated with hormonal and metabolic derangements, the "stress response," which results from activation of the hypothalamic-pituitary-adrenal axis and the sympathetic system. It is characterized by systemic release of catecholamines, cortisol, and cytokines.[19] The stress response is associated with increased catabolism, immunosuppression, poor postoperative outcomes, and prolonged recovery.[20,21] RA surpasses general anesthesia in ability to minimize the stress response.[19,22] RA blocks the afferent neural transmission from reaching the central nervous system and activating the stress response, and by blocking descending efferent activation of the sympathetic

nervous system.[22-24] In clinical practice, RA has been shown to be superior to systemic opioids alone in thoracic, abdominal, gynecological, and orthopedic surgeries.[25-28] Studies have consistently shown RA to reduce postoperative pulmonary, gastrointestinal, and cardiac morbidities. Furthermore, there is evidence that RA decreases postoperative morbidity and mortality, and shortens postoperative hospitalization.[29-32]

Regional approaches including epidural and TAP blocks are considered key elements in “fast-track” protocols for patients recovering from colorectal surgeries because they facilitate recovery and shorten hospitalization.[33] Thoracic epidural analgesia reduces sympathetic outflow from T6-L12, speeds return of gastrointestinal motility by as much as 3 days.[34,35] RA also reduces consumption of opioids, a major risk factor for postoperative nausea and vomiting, which delays resumption of oral diet. Improved intestinal blood flow may also improve anastomotic healing.[36,37]

Pulmonary complications are common side effect of thoracic and major abdominal surgery, in fact occurring more often than cardiac complications.[38] Important complications include atelectasis, pneumonia, and respiratory failure — and are associated with morbidity, prolonged hospital stay, and increased cost of care.[39] Inadequate analgesia also leads to ineffective breathing ("splinting"), characterized by rapid and shallow breathes which itself contribute to atelectasis, impaired gas exchange, and inability to clear secretions. The use of RA reduces pulmonary complications in patients recovering from thoracic and abdominal surgeries by providing excellent analgesia, preventing “splinting,” and thus improved respiratory mechanics.[40-43]

The most serious opioid-induced complication is respiratory depression. Respiratory depression is the main fatal hazard of opioid use and has been identified as a safety target by the Joint Commission on Hospital Accreditation.[57] Supporting this concern, a study conducted in United Kingdom ranked opioids as the second most common cause of adverse events in hospitalized patients.[58] The current national goal of better controlling postoperative pain by making it a quality indicator is likely to increase opioid use — and almost surely also increase associated complications.

Both hypdrophilic (i.e., morphine) and lipophilic (i.e., fentanyl) opioids promote respiratory depression by: 1) systemic uptake via epidural venous plexus; and 2) arachnoid penetration and cephalad spread. The result is a dose-dependent reduction in responsiveness of brainstem respiratory centers to carbon dioxide partial pressure (PCO_2) with opioids. This is clinically manifested as an increase in resting PCO_2 and a shift in the CO_2 response curve.[59,60] We will also evaluate hypoxic events in this patients and compare the effect of opioid sparing on these events.

Postoperative nausea and vomiting (PONV) is a common complication which causes considerable patient discomfort and lowers patient satisfaction.[61] In patients given epidural opioids, it is caused by upward migration of opioids in CSF which then stimulate the chemoreceptor trigger zone of the medulla.[62] Consequently, PONV remainscommon during epidural analgesia, with a reported incidence of up to 70%.

Opioids also enhance sphincter tone and reduce peristaltic contraction. Delayed gastric emptying is caused by decreased motility, increased antral tone, and increased tone in the first part of the duodenum. Delay in passage of intestinal contents leads to greater absorption of water, increased viscosity, and desiccation of bowel contents — which in turn causes constipation and contributes to postoperative ileus. [63] Postoperative ileus, with an incidence of 4.5%, prolongs hospital stay and increases hospital costs.[64] Opioids also inhibit urinary bladder function, thus increasing the risk of urinary retention.

C. Epidural Analgesia and side effects

Epidural analgesia (EA) is an indispensible part of modern perioperative pain management because it provides better postoperative analgesia after abdominal surgery than systemic opioids.[26] Commonly, a small dose of local anesthetic-opioid combination is injected through a catheter into the epidural space, then the mixture diffuses across the dura, reaching spinal nerve roots, dorsal root ganglion, or the spinal cord to block afferent pain signals to attenuate the surgical stress response and provide excellent analgesia.[44] Meta-analysis shows that epidural analgesia reduces mortality by a third compared with systemic opioids; it also decreases cardiovascular and pulmonary morbidities in high-risk

patients, speeds return of bowel function, and decreases the risk of venous thromboembolism. EA also enhances patient satisfaction compared with parental opioids.[45]

Despite its widespread use, EA is has several limitations. First, locating the epidural space (ES) by loss-of-resistance is a blind procedure and is operator dependent.[46] Anatomical variations from age-related vertebral changes, spine pathologies (i.e. scoliosis), previous back surgeries, body habitus, and normal variations in skin-to-epidural space all contribute to difficult epidural catheter insertion. The ES is a potential space consisting of a labyrinth of epidural fat, lymphatics, venous plexus, spinal nerves, and compartments separated by tissue band which make location of catheter tip hard to control; a consequence can be nonuniform spread of anesthetics and subsequent unilateral or failed block.[47,48]

A further problem is that epidural catheter migration is common, with incidence of 36%, and is due to body movement and oscillations of CSF.[49,50] The tip can migrate out of the epidural space via intervertebral foramen (resulting in epidural failure), laterally (result in unilateral block), into subarchnoid space (resulting high or total spinal), or into epidural vein (result in systemic anesthetic toxicity).[49,51,52] All of these factors contribute to a high failure rate, reported to be 23-30%[50,53]

There are also situations in which patients are unable to receive epidural anesthesia, or epidural blocks are especially prone to failure. Anticoagulated patients, for example, are not ideal candidates for neural anesthesia due to risk of epidural hematoma. Patients with history of chronic back low back pain, spine pathologies (scoliosis, spina bifida), or history of back surgery are also at increased risk of failed epidural blocks. In patients with previous spine surgeries, epidural scarring or altered anatomy may make the ES nearly impossible to locate; and even when an epidural catheter can be inserted, scarring of ligamentum flavum often reduces the size of the epidural space leading to patchy blocks.[51]

Serious complications from EA are fortunately rare. Nonetheless, epidural analgesia can cause side effects either from administered medications or from injury from

epidural vessels and neurological structures. Epidural analgesia also causes hypotension in about 3-7% of patients[54] consequent to blocking sympathetic outflow which promotes venous and arterial vasolidation and a “functional” hypovolemia. Although hypotension is usually transient, strokes have been reported in patients with low reserve.[55] More commonly, hypotension prompts clinicians to at lease temporarily cease local anesthetic administration and to give fluids or vasopressors.[56] Typically, opioids are substituted during hypotensive periods, at least transiently exposing patients to opioid-related complications.

Although rare, neurologic complication consequent to neuraxial blocks can be devastating. Examples include epidural hematoma, epidural abscess, and postdural puncture headache.[65] With widespread use of anticoagulants, patients are at increased risk of developing epidural hematoma from initial needle insertion to catheter manipulation. If unrecognized, epidural hematoma can cause cord compression and permanent paraplegia. Postdural puncture headache, although rare (~1%), cause significant morbidity, require additional treatments (i.e., bed rest, blood patch), prolong hospital stays, and may persist for months.[66]

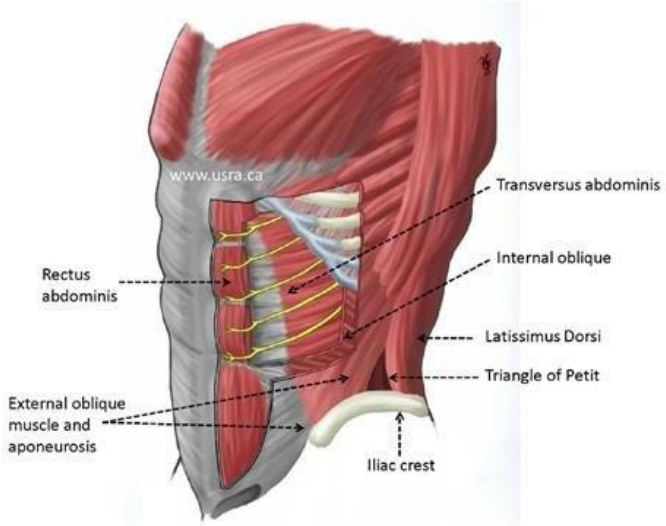
Including opioids to epidural local anesthetics has become the standard for providing epidural analgesia. Beneficial therapeutic effects of epidural opioids as a result of improved analgesia include improvement in pulmonary function, modification of the endocrine-metabolic stress response, improvement in time to ambulation, decreased morbidity, and shorter hospital stay. The epidural administration of opioids is associated with potential side effects and complications, the most serious potential side effect being that of respiratory depression. This, as well as most of the other potential opioid-related side effects is associated with epidural opioid analgesia. A consequence of thesetoxicities and side effects is that epidural sometimes needs to be stopped at least temporarily, thus reducing the analgesic benefits of RA.

In summary, epidural analgesia provoke numerous limitations and severe complications that cause substantial patient morbidity. Nonetheless, epidural analgesia provides superior pain control and causes fewer side effects than systemic opioids.

Epidural analgesia also delays discharge from hospital, increases the cost of care, and reduces patient satisfaction.

D. Transverses Abdominis Block

The Transversus Abdominis Plane (TAP) block, first described by Rafi in 2001, is an alternative approach to providing post-operative analgesia to the anterior abdominal wall **(Figure 1)**.[67] For a TAP block, local anesthetic is injected into the plane between the transversus abdominis and internal oblique muscles to interrupt the innervation of afferent nerves (T6-L1) of the anterior abdominal wall including the parietal peritoneum, muscles, and skin.



Picture 1. Abdominal wall

Complications related to TAP blocks are rare. Early reports of liver laceration from the block were likely from a combination of landmark technique and improper use of ultrasound.[68] The TAP block is easier to perform than epidural anesthesia (especially with ultrasound guidance), safer, relatively inexpensive, and can be used safely in patients who are anti-coagulated. Local anesthesia to the TAP can be given as a “single shot” or via continuous local anesthetic infusion. Widespread clinical TAP catheter use is limited because of easy dislodgment of catheter and close vicinity to surgical site.

TAP appear to be safe and effective as part of multimodal analgesia for various abdominal surgeries including open appendectomy, hysterectomy, caesarean delivery, abdominoplasty, prostectomy, renal transplant, and laparoscopic surgeries.[69-76] It is even possible to use TAP as sole anesthetic technique in open abdominal procedures.[77,78] TAP blocks in colorectal surgery requiring a midline incision reduce postoperative opioid consumption, PONV, and sedation.[79]

TAP blocks only provide somatic pain relief whereas epidural anesthesia also provides visceral and somatic relief. TAP blocks nonetheless provide effective analgesia and reduce opioid requirements. Furthermore, retention of sensory and motor function lower extremities facilitates early ambulation and presumably reduces the risk of falls.

E. Exparel

Use of local anesthetics in postsurgical pain is limited because the duration-of-action of current local anesthetics is short. Effective postoperative analgesia thus usually requires insertion of a catheter and continuous or repeated anesthetic administration.

Exparel (Exparel®, bupivacaine liposome injectable suspension, Pacira Pharmaceuticals Inc., Parsippany, NJ, USA) is a sterile, non-pyrogenic white to off-white preservative-free aqueous suspension of multivesicular liposomes (DepoFoam® drug delivery system) containing bupivacaine. Exparel is a liposome injection of bupivacaine, an amide-type local anesthetic, indicated for administration into the surgical site to produce postsurgical analgesia and intended for single-dose administration. Depofoam technology is based on multiple microscopic spherical particles with many aqueous chambers separated by lipid membranes. When refrigerated, the particles are stable; but after injection of Exparel into soft tissue, bupivacaine is released from the multivesicular liposomes over a period of time. The components of Depofoam particles are non-toxic and clinical trials have demonstrated no adverse events. Furthermore this technology previously has been safely used in different settings and provided sustained release in other target areas.

Various doses of Exparel were compared with plain bupivacaine in patients having inguinal hernia repairs. Evaluations revealed that Exparel administration produces dose-dependent increases in plasma bupivacaine concentrations, and that the half-life of

Exparel was almost twice that of plain bupivacaine. However, maximum plasma concentrations were similar with plain bupivacaine and Exparel. Studies in other surgical models demonstrated similar results, and analgesia lasting up to 72 hours. Bupivacaine is metabolized through hepatic pathways, hepatic insufficiency thus increases the risk of toxicity.

The clinical efficacy of Exparel has been studied in number of clinical trials. In wound infiltration for hemorrhoidectomy, 189 patients were randomized to Exparel or placebo. Significant reductions in pain scores were seen at each measurement time points for 72 hours. Patients given Exparel required 45% less opioid, and the first opioid dose was almost 12 hours later in Exparel group. In a different study performed in patients having bunionectomies, cumulative pain scores were lower, and the time to first opioid use was significantly prolonged by Exparel. Furthermore, Exparel has also been investigated and demonstrated significant analgesic effect in patients having knee arthroplasty, breast augmentation, and hernia repair. Surgical wound infiltration was also studied in 10 clinical trials, which showed that cumulative pain scores were improved with Exparel through 24-72 hours. However, TAP studies with Exparel in abdominal surgeries are mainly retrospective, with limited number of patients. None of these studies directly compare TAP and epidural analgesia.

F. Pharmaco-economics

Exparel costs about $300 per vial, which is substantial, and some institutions consequently regulate its use. However, in retrospective study demonstrated significant cost effectiveness with Exparel when compared with epidural. There is potential economic benefit of using EXPAREL in TAP blocks. Even after agreeing with the efficacy of EXPAREL, one reason for its slow adaptation into mainstream acute pain practice is the drug would drive up cost of heath care. In addition, it has been documented that EXPAREL-based multimodal analgesia was associated with lower cost and length of hospital stay ($8766, 2 days) versus opioid-based analgesia ($11850, 4.9 days) in patients after open colectomies.[80]

Due to the long history on epidurals, there might be a underestimation of the overall cost associated with epidurals. Schuster et al. conducted a retrospective cost analysis on the cost drivers of total expense of managing a patient-controlled epidural in a variety of surgeries and discovered that 51% of the cost was staff related and 15% was related to PCA pumps and pump materials.[81] In many hospitals, patients with epidurals are continuously monitored by both ward nurses and acute pain service residents for opioid and epidural related side effects. These costs can potentially be reduced or eliminated by the opioid-free Exparel. More time and resources can thus be freed to care for more patients in need.

F. Rationale of the study

The recent enhancement of conventional bupivacaine with encapsulated bupivacaine much prolongs the duration-of-action and resulting pain control with a single application. TAP blocks appear to be easier to perform than epidurals (especially with ultrasound guidance), safer, relatively inexpensive, and can be used safely in patients who are anti-coagulated.

Only three studies have compared the analgesic effects of TAP blocks and epidural catheters.[82-84] Niraj et al. compared the analgesic effects of bilateral subcostal TAP catheters and epidural catheters and reported a success rate of 78% for epidural versus 63% for TAP, although the results were not statistically significant.[82] Another study in 2013 did not show any significant difference in analgesic effects of bilateral TAP catheters and epidural catheters.[83] And finally, in a recent study, single-injection TAP was compared with IV opioid and epidural analgesia. The authors found that single-injection subcostal TAP blocks were more effective than IV opioid analgesia, while continuous thoracic epidural analgesia was more effective than the single-injection subcostal TAP block. Existing studies suffer from small sample size and inconsistent conclusions. Experts in regional anesthesia have emphasized the need for well-powered studies comparing the different methods.[85-88]

In our institution we retrospectively investigated patients who received TAP with Exparel for abdominal surgery and compared it with patients who received epidural. 318

patients were propensity matched on 18 potential factors among three groups (106 per group): 1) TAP infiltration with bupivacaine liposome; 2) continuous Epidural analgesia with plain bupivacaine; and; 3) intravenous patient-controlled analgesia (IV PCA). TAP infiltration were non-inferior to Epidural on both primary outcomes (p<0.001). TAP infiltration were non-inferior to IV PCA on pain scores (p=0.001) but not superior on opioid consumption (p=0.37) (Figure 1). TAP infiltration with liposomal bupivacaine and continuous epidural analgesia were similar in terms of pain and opioid consumption, and not worse in pain compared with IV PCA. Which demonstrated that TAP infiltrations with exparel are a reasonable alternative to epidural analgesia in abdominal surgical patients.

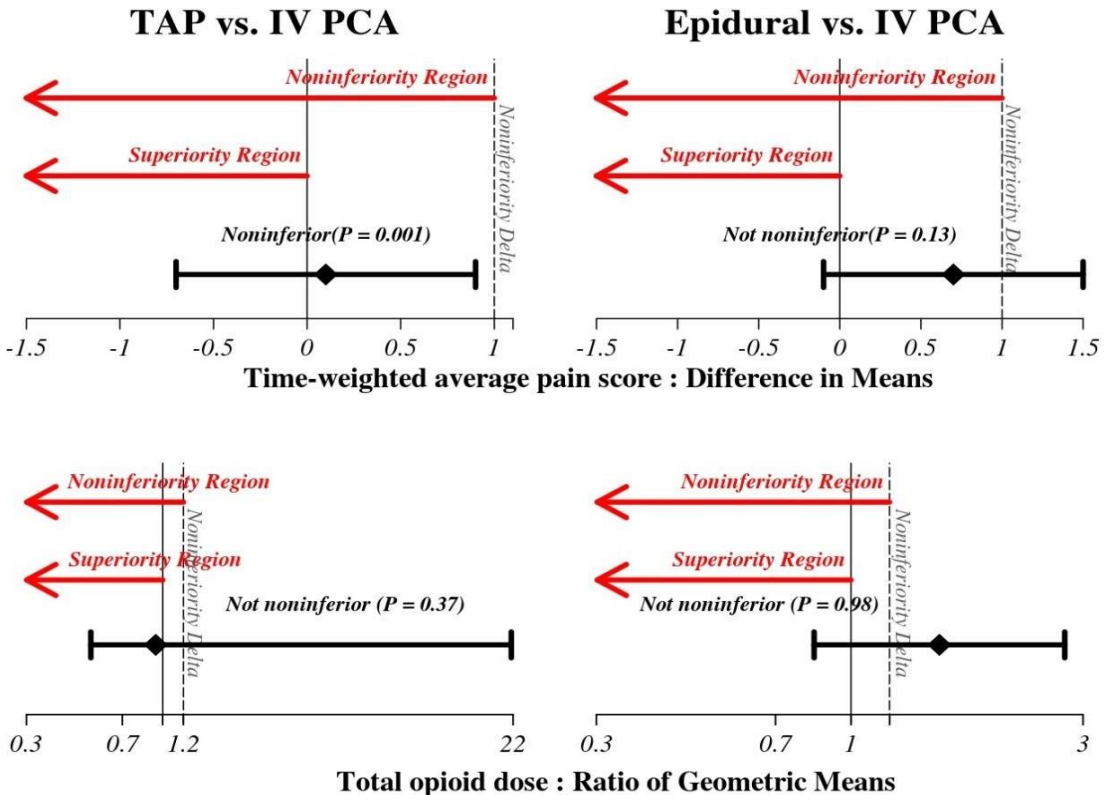


Figure 1 Results for comparison TAP infiltration and Epidural patients on postoperative time-weighted average pain score in the 0-10 VRS pain scale and intravenous morphine equivalent dose of opioid within 72 hours of the surgery.

Furthermore, preferable because they are easier to perform and thought to be safer.

2. Study Objectives

We will prospectively compare the analgesic efficacy of TAP blocks with liposomal bupivacaine (Exparel) and continuous epidural blocks in patients who are scheduled for major lower abdominal surgery. Specifically, we will test the primary hypothesis that TAP blocks with single-shot liposomal bupivacaine are noninferior to continuous epidural analgesia for pain control and opioid consumption in patients recovering from major lower abdominal surgery.

The proposed research will have the following aims, all of which will be assessed over 72 hours or the duration of hospitalization if shorter:

Primary Aim.

To assess whether TAP block with Exparel is noninferior to continuous epidural analgesia on pain management, defined as noninferior for both pain control and total opioid consumption for 72 hours, in patients who had major lower abdominal surgery. We define noninferiority as no worse than 25% greater opioid consumption and no worse than 1 point higher in pain score. We choose a 1 point delta for VRS pain score since that is approximately half as large as a delta we would use to assess superiority, and it is also about half of the expected standard deviation in the VRS pain score, both standard methods for choosing a noninferiority delta.

Hypothesis. Bilateral TAP blocks with single-shot liposomal bupivacaine are noninferior to continuous epidural analgesia for both pain control and opioid consumption in patients recovering from major lower abdominal surgery.

Total opioid consumption, in morphine equivalents, will be the major measure of opioid use. However, we will also record the number of times analgesic given for breakthrough pain. Our major outcome for pain will be time-weighted pain scores from discharge from the PACU until 72 hours after the end of surgery. PACU pain scores will also be compared separately. Sedation will be determined and recorded at roughly 4-hour by ward nurses per clinical routine.

Secondary Aims.

Secondary Aim 1: To assess the effect of TAP block with Exparel and epidural analgesia on activity after surgery.

Hypothesis. TAP block with Exparel will have increased amount of time spend sitting or lying with epidural patients.

ViSi mobile (Sotera Wireless) patient monitoring system a platform for comprehensive vital sign monitoring will be used to quantify patient activity over the initial 72 postoperative hours. This system continuously measures position (lying versus sitting) and activity.

Secondary Aim 2: To evaluate TAP block with Exparel and epidural analgesia on opioid related side effect.

Hypothesis. Patients in TAP group have fewer opioid-related side effects than epidural group.

We will use a validated composite outcome, Opioid–Related Symptom Distress Scale (ORSDS), to evaluate opioid-related side effect.[89] ORSDS is 4-point scale that evaluates 3 symptom distress dimensions (frequency, severity, bothersome 4-point scale that evaluates 3 symptom distress dimensions (frequency, severity, bothersomeness) for 12 opioid related side effects. ORSDS questionnaire will be administered by a trained research fellow on first, second, and third postoperative mornings while patients remain hospitalized**.**

Secondary Aim 3: To assess hemodynamic instability TAP block with Exparel and epidural analgesia.

Hypothesis. Patients in TAP group will have higher blood pressure and less hemodynamic instability compared to epidural patients. Hypotension will be defined as MAP hypotension MAP < 55 mmHg and SBP hypotension defined as SBP < 80 mmHg.

ViSi mobile (Sotera Wireless) patient monitoring system will be used to obtain vital signs including beat-to beat noninvasive blood pressure of the patient for 72 hours.

Secondary Aim 4: To assess Quality of recovery after anesthesia with TAP block Exparel and epidural analgesia.

Hypothesis. Patients in TAP group will have higher quality of recovery score than epidural patients.

Quality of recovery after anesthesia and surgery is an important measure of the early postoperative health status of patients, and the Quality of Recovery scale is highly validated.[90] Patients will be questioned on morning of POD 1 and 3.

Secondary Aim 5. To assess length of stay in TAP block with Exparel and epidural analgesia patients after surgery.

Hypothesis. Patients in Epidural group will have prolonged length of hospital stay compared to epidural patients.

Secondary Aim 6. To assess the cost-effectiveness of TAP block with Exparel after surgery.

Hypothesis TAP block with Exparel reduces the cost of care by decreasing opioid-related side effects and better maintaining hemodynamic stability.

Exploratory

Exploratory Aim 1. To compare TAP block with Exparel and epidural analgesia on postoperative opioid-related hypoxic events.

Hypothesis. TAP block with Exparel reduces hypoxic events compared to epidural analgesia patients.

Patients will have continuous pulse-oximeter monitoring and recording. Nurses and the study personal will be blinded to data on the monitor and standard of care will be provided. Data from the monitor will be downloaded daily for 72 hours postoperatively, incidence of hypoxia and the time spend hypoxic will be determined. We will be using ViSi mobile (Sotera Wireless) patient monitoring system a platform for comprehensive vital sign monitoring. This system will measure 3 lead ECG, SpO2 and number of respirations continuously. The outcome will be area-under-the-curve for saturation over time with the threshold set at 90%.

Exploratory Aim 2. To compare TAP block with Exparel and epidural analgesia on persistent postoperative pain.

Hypothesis. TAP block with Exparel reduces persistent postoperative pain (defined by pain at incision at three month follow up) similar to epidural analgesia patients.

Patients were also contacted by one of the investigators at 3 and 6 months after discharge to evaluate whether persistent surgical pain. Presence and VAS score for persistent surgical pain and effect on MBPI will be asked to rate. DN4 Test will be used to evaluate postoperatively at 3 months for defining the type of pain.[91]

3. Method and Study Design

A. Study Overview

We propose a randomized trial comparing TAP blocks with Exparel to continuous epidural blocks in patients having elective lower-abdominal surgery. The study will be performed at multiple sites including various Cleveland Clinic hospitals.

B. Setting and Population

Inclusion criteria:

(1) Written informed consent;

(2) 18-85 years old;

(3) ASA Physical Status 1-3;

(4) Scheduled for elective open or laparoscopic abdominal surgery, including colorectal and hysterectomy surgeries;

(5) Anticipated hospitalization of three nights;

(6) Expected requirement for parenteral opioids for at least 72 hours for postoperative pain;

(7) Able to use IV PCA systems.

Exclusion criteria:

(1) Hepatic disease, e.g. twice the normal levels of liver enzymes;

(2) Kidney disease, e.g. twice the normal level of serum creatinine;

(3) Bupivacaine sensitivity or known allergy;

(4) Women who are pregnant or breastfeeding;

(5) Anticoagulants considered to be a contraindication for epidural or TAP blocks.

(6) Surgeries with high port sites will be excluded

C. Withdrawal Criteria

Patients will be free to withdraw from study at any time. Patients will also be

removed from study at any time for adverse events, or deemed necessary for patient safety.

Protocol

After eligibility is confirmed, patients will receive complete information about the study both verbally and in writing. Informed consent must be obtained from the patients prior to randomization and study-specific procedures. Research fellow will also apply an 8-item STOP-BANG questionnaire. Randomization will be web-based and independent to investigators interference.

Randomization (1:1) will be web-based and initiated at induction of anesthesia; allocation will thus be concealed from investigators. Randomization will be stratified based on chronic opioid use, defined by opioid use for more than 30 consecutive days within three preoperative months, at a daily dose of 15 mg or more of morphine or equivalent.

All blocks will be performed preoperatively by attending anesthesiologists or regional anesthesia fellows who are experienced in epidural blocks and TAP blocks. Premedication will be administered at the discretion of the attending anesthesiologist and standard monitors will be used. All the patients will receive 1000 mg oral acetaminophen one hour before surgery and they will receive 500 mg every 6 hours for 72 hours after surgery starting with oral intake.

Patients will be randomly assigned to: 1) Epidural catheter, 2) Bilateral TAP block with Exparel. Randomization will be stratified by open and laparoscopic procedures in addition to chronic opioid use. An in-plane ultrasound will be used in TAP block procedure. Once the target area is positioned, plain bupivacaine 0.25 %, 20 ml will be given to open the space and then single dose (10 ml) of EXPAREL mixed with (10 ml) saline will be injected in each side. Total dose of Exparel will be 20 ml. Epidural catheters will be inserted preoperatively. Once an epidural catheter is successfully positioned, an infusion will be initiated intraoperatively. Bupivacaine standard solution without additives will be prepared for each patient in epidural group.

Standard general anesthesia will be given using propofol or etomidate, fentanyl, rocuronium for induction and sevoflurane or isoflurane. Intraoperative analgesic use will be limited to short acting opioids. Postoperatively, patients will be given intravenous patient-controlled analgesia. Hydromorphone will be the default drug, but fentanyl will be substituted if necessary. Clinicians will adjust analgesic management as necessary in an effort to keep verbal response pain scores (details below) <4. If patients would not use the PCA for more than 2 hours, PCA will be deceased and it will be changed to PRN hydromorphone or fentanyl. Nurses will adjust analgesic management as necessary in an effort to keep verbal response pain scores <4. Blinded clinicians to the study will adjust epidural infusion rates.

Other anti-inflammatory drugs will not be used intraoperatively or for the initial 72 postoperative hours. A single dose of dexamethasone (4-8 mg) will be permitted for PONV prophylaxis for patients with Apfel risk score of 2 or more, and inhaled steroids will be permitted as necessary to treat reactive airway disease. Other opioid sparing medications like gabapentin, pregabalin, ketamine or lidocaine patch will also not be permitted through the initial 72 postoperative hours.

Clinical evaluators for the outcomes will be blinded to study aim and Pharmacy personnel not involved in evaluations will prepare the study drugs. Patients will be continuously monitored and recorded with a wireless monitor starting after extubation in the operating room. Clinicians including nurses will be blinded to monitoring and will be required to perform their standard of care management after surgery.

Patients will be allowed to receive prophylactic anti-emetic (first choice ondansetron) intraoperatively based on the risk assessment for nausea and vomiting. Postoperative anti-emetics for symptomatic treatment will also be allowed; again ondansetron will be the first choice.

Measurements

Demographic and Background Information:

Demographic data to be obtained includes height (cm), weight (kg), age (yr), gender, (ASA) physical status, self-declared ethnicity, and the specific type of procedure will be recorded. Patients will be questioned for social history (tobacco) and medical history (pulmonary disease, kidney disease, diabetes mellitus, neurological disease, chronic pain conditions, illegal drug usage, alcohol abuse, myocardial infarction, previous surgery or stent placement and medications usage). Available preoperative laboratory tests and medication list will be recorded. Individual risk for nausea and vomiting will be determined using the Apfel score. Patients excluded for any reason including technical or contraindication will be recorded for both groups.

ViSi mobile (Sotera Wireless) patient monitoring system will be used to continuously record noninvasive blood pressure, patient activity, posture, 3-lead ECG, SpO2, and respiratory rate. Data will be recorded at one-minute intervals and downloaded daily to a laptop.

Opioid requirements will be measured as the total amount of opioids (converted to morphine sulfate equivalents) used intraoperatively and during the first 72 postoperative hours. Use of PCA and discontinuation will be recorded. Pain Scores after surgery with be measured using a Verbal Response Scale (VRS). VRS is a scale from 0 to 10 where 0 signifies no pain and 10 signifies worst pain ever experienced. The VRS will be recorded every 30 minutes in the recovery area for the first 2 hours, then every ≈4 hours thereafter while awake for 72 hours. Extra boluses of local anesthetics or block failure will be notified to acute pain service and will be documented in EPIC.

Patient satisfaction with their pain treatment will be questioned after 72 hours/discharges using 0-100 scales and we will also use Myles QoR scale to formally evaluate quality of recovery. Myles QoR scale is a validated scoring system allows quantification of patient's early postoperative health status, which is also a description of quality of recovery. We will record the hospitalization period.

Failure to meet four criteria was determined as the factors delaying discharge: (1) adequate analgesia (defined as NRS <4); (2) independence from intravenous opioids for at least 12 h; (3) ability to independently stand and sit down (evaluated with the Timed

Up and Go test); and (4) unassisted ambulation of at least 30 m (evaluated with the 6-min walk test). Blinded investigator will evaluate patients for discharge readiness and patients having all four factors will be accepted as discharge ready.

Data obtained from electronic medical records will include: operation time, surgery type, intraoperative opioid consumption, postoperative opioid consumption in PACU and in ward, breakthrough pain medication requirements, pain scores in PACU and ward, requirement of oxygen in PACU and ward, pruritus, requirement of antihistaminic medications, requirement of naloxone, itching, ambulation time, flatus, ileus, bowel movements (first time, all bowel sounds at all quadrants), constipation, length of stay and any side effects or complications. Patient functionality will also be recorded including, bathing, toileting, walking and moving.

We will also record any interruptions with comments in epidural group administration because of hemodynamic instability and lower extremity weakness. Blood pressure will be continuously monitored with VISI monitor system.

Brief Pain Inventory and the Short Form 12 health survey (SF 12) will be completed before surgery, and at the 90-day follow up. Brief Pain Inventory is a practical method of evaluating pain severity and impact on patient function. BPI includes four rating pain intensity, and seven covering the impact of pain. Intensity is recorded on an ordinal scale from zero (no pain) to ten (worst imaginable pain). Impact of the pain section these ratings are made on zero-to ten numeric scales running from no interference to complete interference. The Short Form 12 health survey is an abbreviated version of the SF-36 health survey, a well-established instrument to assess psychological and physical aspects of health related quality of life.

G. Data Analysis

Randomized groups will be compared for baseline balance using standard descriptive statistics and the standardized difference (difference in means or proportions divided by the pooled standard deviation).

Primary Aim. TAP with Exparel will be considerable noninferior to continuous epidural analgesia (and vice versa) on pain management if found noninferior on each of total opioid consumption and mean pain score in the first 72 hours post-op. Noninferiority deltas are defined a priori as no worse than 25% higher in opioid consumption and no worse than 1 point in pain score. Overall alpha will be 0.05, and thus 0.025 in each direction of testing. No correction to the significance criterion will be made for assessing 2 primary outcomes since both are required to be noninferior in order to reject the null hypothesis and claim one intervention noninferior on pain management.

We will assess noninferiority for opioid consumption by first estimating the treatment effect (TAP with Exparel minus continuous epidural analgesia, and vice versa) on log-transformed opioid consumption in a linear regression model and then conducting 1-tailed tests to assess whether the exponentiated difference, i.e., ratio of geometric mean, is less than the noninferiority delta of 1.25.

We will assess noninferiority for mean pain score over time by first estimating the treatment effect (TAP with Exparel minus continuous epidural analgesia, and vice versa) on VRS pain score in a repeated measures linear model adjusting for within-subject correlation (R matrix autoregressive (1) structure) across the times. We will then use the estimated treatment effect (collapsed over time) and its standard error to conduct 1-tailed tests to assess whether the difference in means is less than the noninferiority delta of 1.

Secondary aims. Standard statistical analyses will be used.

Interim analyses for efficacy and futility will be conducted at each 25% of the planned enrollment (N=160, 320, 480 and 640) using a group sequential design with a gamma spending function (gamma = - 4 for efficacy and -2 for futility). The probability of crossing a boundary at the 1st, 2nd, 3rd and last analyses will be 8%, 29%, 38% and 25%, respectively, if the alternative hypothesis is true. *Thus, there is a 75% chance of crossinga boundary (efficacy or futility) by the third look (N=480).* We chose a design with 3 interim analyses and a final as opposed to fewer or more interim looks based on both practical and statistical grounds (allowing the chance to stop early, middle or late if warranted, but not too many looks as not much is gained by a larger number). The study

has been designed with non-binding statistical boundaries, such that the monitoring committee is not required to stop the study after crossing an efficacy or futility boundary (i.e., it will not affect the stated type I or type II errors to continue the study after a boundary has been crossed).

H. Sample Size Considerations

Sample size is based on being able to detect noninferiority on both total opioid consumption and pain score in the first 72 hours with about 90% overall power (90% for opioid consumption and 99.5% for pain score; overall power = 0.90 x 0.995 assuming independence) at the overall 0.025 significance level. In our retrospective data we observed a coefficient of variation (CV=SD/mean) of about 1.10 for opioid consumption in similar patients. For a single-analysis study we would need a total of 588 patients to have 90% power to detect noninferiority for opioid consumption at the 0.025 significance level assuming a CV of 1.0 and noninferiority delta of 1.25 in ratio of geometric means. A single-analysis total of 588 patients would give over 99.5% power to detect noninferiority in pain score with a delta of 1 point assuming (conservatively) a standard deviation of 2.5 (from prior studies we expect the SD to be closer to 2.0; a total of N= 296 patients would be required for 99% power assuming a SD of 2.0 for pain score). We therefore plan the study to be able to detect noninferiority on both primary outcomes, which is largely driven by opioid consumption.

Planning for a maximum of 3 interim analyses and a final analysis would require a maximum of 640 total patients.

Economic Analysis

A cost-effectiveness analysis will be conducted to determine the optimal strategy for economic outcomes related to pain control and surgery. In a cost-effectiveness analysis, costs are measured in monetary terms and benefits are measured in a unit of effect. For this study, the costs will be considered from the perspective of the hospital. The benefits will be evaluated on the cost to decrease the pain scores by 1 point using the visual analogue scale. For this cost-effectiveness analysis, the incremental difference in costs and effects between interventions being evaluated will determine the optimal strategy of

choice.

To undertake this form of analysis, a decision analytic model using Treeage Pro® will be developed. A decision analytic model is a systematic, quantitative approach to decision making and can aid in health-care resource allocation. The decision analytic model will compare two possible intervention arms: A- Exparel, andB-Epidural analgesia. All possible outcomes will be incorporated into the model. Successful epidural placement and all adverse events, including PONV and ileus, will be incorporated as arms within the models. LOS, labor and 30 day adverse events will be incorporated at the terminal nodes. A simplified decision tree is presented in Figure 1. A hospital/payer perspective will be adopted and include all relevant costs and outcomes. Only costs and benefits relevant to the interventions in question will be included. All outcome probabilities used in the model will be determined from the clinical trial.

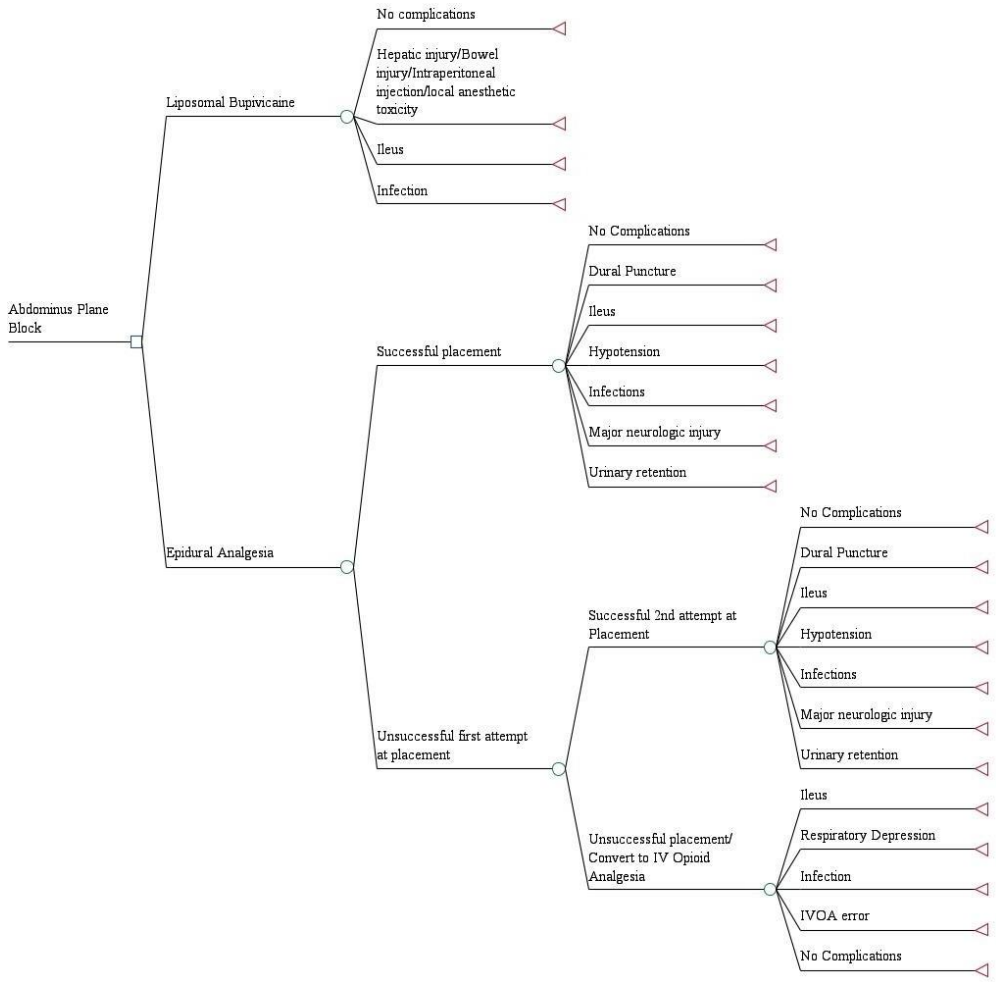


Figure 1 – Skeleton Decision Tree – Exparel vs Epidural Analgesia

Costs to be included will be the costs of the intervention drugs, cost of consumables, the cost of adverse events, cost of any labor including nursing and physician time in the OR, PACU and on the floor, and the cost of any healthcare resources required in the 30 days post-surgery. These resources may include ER visits, physician visits or hospitalizations attributable to the procedure. Drug costs will be valued using the average wholesale acquisition cost as reported from the Elselvier Rx Verify database. Consumable costs will be sourced from supply management and verified from the published literature. The value of LOS will be valued based on Medicare/Medicaid reimbursement schedules. Adverse event costs will be sourced from the clinical trial where available and verified using published literature. Labor prices will be sourced from the Bureau of Labor and

Statistics using US averages. All costs will be adjusted to the same base year using the Medical Component of the Consumer Price Index. As costs and effects are being calculated for only a short time frame, no future discounting will be used.

The determined costs and effects for each arm of the decision tree will be incorporated. The analysis of the model will use the costs, effects and probabilities of each arm of the decision tree. The analysis outcome will be a cost-effectiveness ratio for each arm. The incremental cost-effectiveness ratio will be calculated for the interventions. Depending on the results, one intervention may be dominated in terms of cost and effect or the optimal strategy may be dependent on willingness to pay for additional units of effect.

The initial analysis would use direct clinical trial data. One criticism of clinical trial data, especially when it is used in an economic evaluation is that its outcomes can't always be generalized to other settings. Through the use of economic modeling, clinical trial outcomes can be modeled to real world conditions. Models can also extrapolate data beyond the clinical trial, link intermediate clinical endpoints to final outcomes, andsimulate head to head comparisons of interventions where a trial does not exist. For thisstudy, complex sensitivity analysis will be conducted to test the robustness of the resultsto variability and uncertainty in the models values and its effect on the choice of optimal strategy. The model will be populated with not just point estimates, but with the range of data values and their associated distributions.

Variability and uncertainty in the model will be analyzed from 3 aspects; variability in the population, uncertainty in the structure of the model, and uncertainty of the variables used within the model. Variability of the population will be tested using a Monte Carlo Microsimulation. This analysis involves running one patient at a time through the model with the events based on the underlying probabilities and a random number generator within the model. This analysis simulates differences in populations and the distribution of potential outcomes including optimal intervention choice can be plotted. Uncertainty within the model will be analyzed using one-way sensitivity analysis. This analysis involves varying the value of one variable at a time within the predetermined range. From this analysis will be conducted where one value will be varied at a time. From this analysis, the variables who are the biggest drivers of changes in the model will be identified and

summarized with a tornado diagram. These drivers will be compared to the drivers identified from the retrospective analysis to ensure uncertainty surrounding the values of these variables is adequately addressed.

To test the uncertainty of the variables used in the model, probabilistic sensitivity analysis will be conducted. This form of analysis allows the uncertainty of all the variables in the model to be assessed at the same time. The values of variables are sampled from the distributions within the model. Using these results, the incremental cost benefit ratios will be determined with confidence intervals. Incremental net benefits will also be determined by determining a cost-effectiveness acceptability curve. This curve summarizes what proportion of time the optimal strategy will indeed be the optimal strategy as it depends on willingness to pay. To further validate the results and support the identification of the optimal strategy, a cost-effectiveness acceptability frontier will be produced along with an expected value of perfect information analysis.

From all the analyses presented above, a transparent, easy to follow cost-effectiveness summary will be produced to aid persons in decision making positions. The summary will include the costs and effects of each intervention, the incremental costs and effects between the interventions, the cost-effectiveness ratio of the interventions, and the incremental cost-effectiveness ratio between the interventions. The uncertainty around the results will also be summarized to show that the optimal strategy is the choice strategy in ‘what’ percentage of time and for ‘what’ variable values and the value of any additional research.

References

1. Buvanendran A, Kroin JS: Multimodal analgesia for controlling acute postoperative pain. Curr Opin Anaesthesiol 2009; 22: 588-93
2. Brennan TJ, Kehlet H: Preventive analgesia to reduce wound hyperalgesia and persistent postsurgical pain: not an easy path. Anesthesiology 2005; 103: 681-3
3. Desborough JP: The stress response to trauma and surgery. Br J Anaesth 2000; 85: 109-17
4. Wilmore DW: From Cuthbertson to fast-track surgery: 70 years of progress in reducing stress in surgical patients. Ann Surg 2002; 236: 643-8
5. Holte K, Kehlet H: Postoperative ileus: a preventable event. Br J Surg 2000; 87: 1480-93
6. Nikolajsen L, Minella CE: Acute postoperative pain as a risk factor for chronic pain after surgery. European Journal of Pain Supplements 2009; 3: 29-32
7. Perkins FM, Kehlet H: Chronic pain as an outcome of surgery. A review of predictive factors. Anesthesiology 2000; 93: 1123-33
8. Apfelbaum JL, Chen C, Mehta SS, Gan TJ: Postoperative pain experience: results from a national survey suggest postoperative pain continues to be undermanaged. Anesth Analg 2003; 97: 534-40, table of contents
9. Phillips DM: JCAHO pain management standards are unveiled. Joint Commission on Accreditation of Healthcare Organizations. Jama 2000; 284: 428-9
10. Weinbroum AA: Non-opioid IV adjuvants in the perioperative period: pharmacological and clinical aspects of ketamine and gabapentinoids. Pharmacol Res 2012; 65: 411-29
11. White PF, Kehlet H, Neal JM, Schricker T, Carr DB, Carli F: The role of the anesthesiologist in fast-track surgery: from multimodal analgesia to perioperative medical care. Anesth Analg 2007; 104: 1380-96, table of contents
12. Benyamin R, Trescot AM, Datta S, Buenaventura R, Adlaka R, Sehgal N, Glaser SE, Vallejo R: Opioid complications and side effects. Pain Physician 2008; 11: S105-20
13. Sacerdote P, Bianchi M, Gaspani L, Manfredi B, Maucione A, Terno G, Ammatuna M, Panerai AE: The effects of tramadol and morphine on immune responses and pain after surgery in cancer patients. Anesth Analg 2000; 90: 1411-4
14. Beilin B, Shavit Y, Hart J, Mordashov B, Cohn S, Notti I, Bessler H: Effects of anesthesia based on large versus small doses of fentanyl on natural killer cell cytotoxicity in the perioperative period. Anesth Analg 1996; 82: 492-7
15. Yeager MP, Colacchio TA, Yu CT, Hildebrandt L, Howell AL, Weiss J, Guyre PM: Morphine inhibits spontaneous and cytokine-enhanced natural killer cell cytotoxicity in volunteers. Anesthesiology 1995; 83: 500-8
16. Boland JW, Foulds GA, Ahmedzai SH, Pockley AG: A preliminary evaluation of the effects of opioids on innate and adaptive human in vitro immune function. BMJ Support Palliat Care 2014; 4: 357-67
17. Lipkind GM, Fozzard HA: Molecular modeling of local anesthetic drug binding by voltage-gated sodium channels. Mol Pharmacol 2005; 68: 1611-22

18. Elkassabany N, Cai LF, Mehta S, Ahn J, Pieczynski L, Polomano RC, Picon S, Hogg R, Liu J: Does Regional Anesthesia Improve the Quality of Postoperative Pain Management and the Quality of Recovery in Patients Undergoing Operative Repair of Tibia and Ankle Fractures? J Orthop Trauma 2015; 29: 404-9

19. Pflug AE, Halter JB: Effect of spinal anesthesia on adrenergic tone and the neuroendocrine responses to surgical stress in humans. Anesthesiology 1981; 55: 120-6

20. Ledowski T, Bein B, Hanss R, Paris A, Fudickar W, Scholz J, Tonner PH: Neuroendocrine stress response and heart rate variability: a comparison of total intravenous versus balanced anesthesia. Anesth Analg 2005; 101: 1700-5

21. Vallejo R, Hord ED, Barna SA, Santiago-Palma J, Ahmed S: Perioperative immunosuppression in cancer patients. J Environ Pathol Toxicol Oncol 2003; 22: 139-46

22. O'Riain SC, Buggy DJ, Kerin MJ, Watson RW, Moriarty DC: Inhibition of the stress response to breast cancer surgery by regional anesthesia and analgesia does not affect vascular endothelial growth factor and prostaglandin E2. Anesth Analg 2005; 100: 244-9

23. Kehlet H: The stress response to surgery, Neural blockade in anaesthesia and pain management. Edited by Cousins M, Brinderbough M. New York, Lippincott-Williams, 1998.

24. Buggy DJ, Smith G: Epidural anaesthesia and analgesia: better outcome after major surgery?. Growing evidence suggests so. Bmj 1999; 319: 530-1

25. Tiippana E, Nilsson E, Kalso E: Post-thoracotomy pain after thoracic epidural analgesia: a prospective follow-up study. Acta Anaesthesiol Scand 2003; 47: 433-8

26. Werawatganon T, Charuluxanun S: Patient controlled intravenous opioid analgesia versus continuous epidural analgesia for pain after intra-abdominal surgery. Cochrane Database Syst Rev 2005: Cd004088

27. Xu J, Chen XM, Ma CK, Wang XR: Peripheral nerve blocks for postoperative pain after major knee surgery. Cochrane Database Syst Rev 2014; 12: Cd010937

28. Rivard C, Dickson EL, Vogel RI, Argenta PA, Teoh D: The effect of anesthesia choice on post-operative outcomes in women undergoing exploratory laparotomy for a suspected gynecologic malignancy. Gynecol Oncol 2014; 133: 278-82

29. Rodgers A, Walker N, Schug S, McKee A, Kehlet H, van Zundert A, Sage D, Futter M, Saville G, Clark T, MacMahon S: Reduction of postoperative mortality and morbidity with epidural or spinal anaesthesia: results from overview of randomised trials. BMJ 2000; 321: 1493

30. Neuman MD, Silber JH, Elkassabany NM, Ludwig JM, Fleisher LA: Comparative effectiveness of regional versus general anesthesia for hip fracture surgery in adults. Anesthesiology 2012; 117: 72-92

31. Guay J, Choi P, Suresh S, Albert N, Kopp S, Pace NL: Neuraxial blockade for the prevention of postoperative mortality and major morbidity: an overview of Cochrane systematic reviews. Cochrane Database Syst Rev 2014; 1: Cd010108

32. Neuman MD, Rosenbaum PR, Ludwig JM, Zubizarreta JR, Silber JH: Anesthesia technique, mortality, and length of stay after hip fracture surgery. Jama 2014; 311: 2508-17

33. Kitching AJ, O'Neill SS: Fast-track surgery and anaesthesia. Continuing Education in Anaesthesia, Critical Care & Pain 2009; 9: 39-43
34. Jorgensen H, Wetterslev J, Moiniche S, Dahl JB: Epidural localanaesthetics versus opioid-based analgesic regimens on postoperative gastrointestinal paralysis, PONV and pain after abdominal surgery. Cochrane Database Syst Rev 2000:Cd001893
35. Moraca RJ, Sheldon DG, Thirlby RC: The role of epidural anesthesia and analgesia in surgical practice. Ann Surg 2003; 238: 663-73
36. Johansson K, Ahn H, Lindhagen J, Tryselius U: Effect of epidural anaesthesia on intestinal blood flow. Br J Surg 1988; 75: 73-6
37. Koolwijk J, Backx JPJM, Bremer RC, Kleinveld S, Noordergraaf GJ: Epidural analgesia as part of a fast track recovery (ERAS) program for elective colonic surgery: just long enough. journal of Anesthesiology and Clinical Science 2013; 2
38. Lawrence VA, Hilsenbeck SG, Mulrow CD, Dhanda R, Sapp J, Page CP: Incidence and hospital stay for cardiac and pulmonary complications after abdominal surgery. J Gen Intern Med 1995; 10: 671-8
39. Sachdev G, Napolitano LM: Postoperative pulmonary complications: pneumonia and acute respiratory failure. Surg Clin North Am 2012; 92: 321-44, ix
40. Liu SS, Block BM, Wu CL: Effects of perioperative central neuraxial analgesia on outcome after coronary artery bypass surgery: a meta-analysis. Anesthesiology 2004; 101: 153-61
41. Nishimori M, Low JH, Zheng H, Ballantyne JC: Epidural pain relief versus systemic opioid-based pain relief for abdominal aortic surgery. Cochrane Database Syst Rev 2012; 7: Cd005059
42. Hausman MS, Jr., Jewell ES, Engoren M: Regional versus general anesthesia in surgical patients with chronic obstructive pulmonary disease: does avoiding general anesthesia reduce the risk of postoperative complications? Anesth Analg 2015; 120: 1405-12
43. Amini N, Kim Y, Hyder O, Spolverato G, Wu CL, Page AJ, Pawlik TM: A nationwide analysis of the use and outcomes of perioperative epidural analgesia in patients undergoing hepatic and pancreatic surgery. Am J Surg 2015; 210: 483-91
44. Hadimioglu N, Ulugol H, Akbas H, Coskunfirat N, Ertug Z, Dinckan A: Combination of epidural anesthesia and general anesthesia attenuates stress response to renal transplantation surgery. Transplant Proc 2012; 44: 2949-54
45. Mann C, Pouzeratte Y, Boccara G, Peccoux C, Vergne C, Brunat G, Domergue J, Millat B, Colson P: Comparison of intravenous or epidural patient-controlled analgesia in the elderly after major abdominal surgery. Anesthesiology 2000; 92: 433-41
46. Drake EJ, Coghill J, Sneyd JR: Defining competence in obstetric epidural anaesthesia for inexperienced trainees. Br J Anaesth 2015; 114: 951-7
47. Hogan Q: Epidural catheter tip position and distribution of injectate evaluated by computed tomography. Anesthesiology 1999; 90: 964-70
48. Hogan QH: Lumbar epidural anatomy. A new look by cryomicrotome section. Anesthesiology 1991; 75: 767-75
49. Bishton IM, Martin PH, Vernon JM, Liu WH: Factors influencing epidural catheter migration. Anaesthesia 1992; 47: 610-2

50. Hermanides J, Hollmann MW, Stevens MF, Lirk P: Failed epidural: causes and management. Br J Anaesth 2012; 109: 144-54
51. Arendt K, Segal S: Why Epidurals Do Not Always Work. Reviews in Obstetrics and Gynecology 2008; 1: 49-55
52. Clarkson CW, Hondeghem LM: Mechanism for bupivacaine depression of cardiac conduction: fast block of sodium channels during the action potential with slow recovery from block during diastole. Anesthesiology 1985; 62: 396-405
53. Thangamuthu A, Russell IF, Purva M: Epidural failure rate using a standardised definition. Int J Obstet Anesth 2013; 22: 310-5
54. Liu SS, Allen HW, Olsson GL: Patient-controlled epidural analgesia with bupivacaine and fentanyl on hospital wards: prospective experience with 1,030 surgical patients. Anesthesiology 1998; 88: 688-95
55. Wu CL, Francisco DR, Benesch CG: Perioperative stroke associated with postoperative epidural analgesia. J Clin Anesth 2000; 12: 61-3
56. Holte K, Foss NB, Svensen C, Lund C, Madsen JL, Kehlet H: Epidural anesthesia, hypotension, and changes in intravascular volume. Anesthesiology 2004; 100: 281-6
57. Fellows I, Bennett T, Macdonald IA: Influence of environmental temperature on the thermoregulatory responses to ethanol, Thermal Physiology. Edited by Hales JRS. New York, Raven Press, 1984, pp 221-3
58. Davies EC, Green CF, Taylor S, Williamson PR, Mottram DR, Pirmohamed M: Adverse drug reactions in hospital in-patients: a prospective analysis of 3695 patient-episodes. PLoS One 2009; 4: e4439
59. Koo CY, Eikermann M: Respiratory effects of opioids in perioperative medicine. Open Anesthesiol J 2011; 5: 23-34
60. Dahan A, Aarts L, Smith TW: Incidence, Reversal, and Prevention of Opioid-induced Respiratory Depression. Anesthesiology 2010; 112: 226-38
61. Gan T, Sloan F, Dear Gde L, El-Moalem HE, Lubarsky DA: How much are patients willing to pay to avoid postoperative nausea and vomiting? Anesth Analg 2001; 92: 393-400
62. Gupta YK, Bhandari P, Chugh A, Seth SD, Dixit KS, Bhargava KP: Role of endogenous opioids and histamine in morphine induced emesis. Indian J Exp Biol 1989; 27: 52-4
63. Panchal SJ, Muller-Schwefe P, Wurzelmann JI: Opioid-induced bowel dysfunction: prevalence, pathophysiology and burden. Int J Clin Pract 2007; 61: 1181-7
64. Asgeirsson T, El-Badawi KI, Mahmood A, Barletta J, Luchtefeld M, Senagore AJ: Postoperative ileus: it costs more than you expect. J Am Coll Surg 2010; 210: 228-31
65. Moen V, Dahlgren N, Irestedt L: Severe neurological complications after central neuraxial blockades in Sweden 1990-1999. Anesthesiology 2004; 101: 950-9
66. Turnbull DK, Shepherd DB: Post-dural puncture headache: pathogenesis, prevention and treatment. Br J Anaesth 2003; 91: 718-29
67. Rafi AN: Abdominal field block: a new approach via the lumbar triangle. Anaesthesia 2001; 56: 1024-6
68. Young MJ, Gorlin AW, Modest VE, Quraishi SA: Clinical implications of the transversus abdominis plane block in adults. Anesthesiol Res Pract 2012; 2012: 731645

69. Niraj G, Searle A, Mathews M, Misra V, Baban M, Kiani S, Wong M: Analgesic efficacy of ultrasound-guided transversus abdominis plane block in patients undergoing open appendicectomy. Br J Anaesth 2009; 103: 601-5

70. Carney J, McDonnell JG, Ochana A, Bhinder R, Laffey JG: The transversus abdominis plane block provides effective postoperative analgesia in patients undergoing total abdominal hysterectomy. Anesth Analg 2008; 107: 2056-60

71. Belavy D, Cowlishaw PJ, Howes M, Phillips F: Ultrasound-guided transversus abdominis plane block for analgesia after Caesarean delivery. Br J Anaesth 2009; 103: 726-30

72. Gravante G, Castri F, Araco F, Araco A: A comparative study of the transversus abdominis plane (TAP) block efficacy on post-bariatric vs aesthetic abdominoplasty with flank liposuction. Obes Surg 2011; 21: 278-82

73. Skjelsager A, Ruhnau B, Kistorp TK, Kridina I, Hvarness H, Mathiesen O, Dahl JB: Transversus abdominis plane block or subcutaneous wound infiltration after open radical prostatectomy: a randomized study. Acta Anaesthesiol Scand 2013; 57: 502-8

74. Soltani Mohammadi S, Dabir A, Shoeibi G: Efficacy of transversus abdominis plane block for acute postoperative pain relief in kidney recipients: a double-blinded clinical trial. Pain Med 2014; 15: 460-4

75. Albrecht E, Kirkham KR, Endersby RV, Chan VW, Jackson T, Okrainec A, Penner T, Jin R, Brull R: Ultrasound-guided transversus abdominis plane (TAP) block for laparoscopic gastric-bypass surgery: a prospective randomized controlled double-blinded trial. Obes Surg 2013; 23: 1309-14

76. Sandeman DJ, Bennett M, Dilley AV, Perczuk A, Lim S, Kelly KJ: Ultrasound-guided transversus abdominis plane blocks for laparoscopic appendicectomy in children: a prospective randomized trial. Br J Anaesth 2011; 106: 882-6

77. Mishra L, Pani N, Mishra D, Patel N: Bilateral transversus abdominis plane block as a sole anesthetic technique in emergency surgery for perforative peritonitis in a high risk patient. J Anaesthesiol Clin Pharmacol 2013; 29: 540-2

78. Lee AR, Choe YS: Anesthesia Experience for Open Gastrostomy With Ultrasound-Guided Unilateral Subcostal Transversus Abdominis Plane Block in a High Risk Elderly Patient: A Case Report. Anesth Pain Med 2015; 5: e24890

79. McDonnell JG, O'Donnell B, Curley G, Heffernan A, Power C, Laffey JG: The analgesic efficacy of transversus abdominis plane block after abdominal surgery: a prospective randomized controlled trial. Anesth Analg 2007; 104: 193-7

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

81. Schuster M, Gottschalk A, Freitag M, Standl T: Cost drivers in patient-controlled epidural analgesia for postoperative pain management after major surgery. Anesth Analg 2004; 98: 708-13, table of contents

82. Niraj G, Kelkar A, Jeyapalan I, Graff-Baker P, Williams O, Darbar A, Maheshwaran A, Powell R: Comparison of analgesic efficacy of subcostal transversus abdominis plane blocks with epidural analgesia following upper abdominal surgery. Anaesthesia 2011; 66: 465-71

83. Rao Kadam V, Van Wijk RM, Moran JI, Miller D: Epidural versus continuous transversus abdominis plane catheter technique for postoperative analgesia after abdominal surgery. Anaesth Intensive Care 2013; 41: 476-81

84. Wu Y, Liu F, Tang H, Wang Q, Chen L, Wu H, Zhang X, Miao J, Zhu M, Hu C, Goldsworthy M, You J, Xu X: The analgesic efficacy of subcostal transversus abdominis plane block compared with thoracic epidural analgesia and intravenous opioid analgesia after radical gastrectomy. Anesth Analg 2013; 117: 507-13

85. Findlay JM, Ashraf SQ, Congahan P: Transversus abdominis plane (TAP) blocks-a review. Surgeon 2012; 10: 361-7

86. Finnerty O, McDonnell JG: Transversus abdominis plane block. Curr Opin Anaesthesiol 2012; 25: 610-4

87. Finnerty O, Sharkey A, Mc Donnell JG: Transversus abdominis plane block for abdominal surgery. Minerva Anestesiol 2013; 79: 1415-22

88. Austin PC: Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Stat Med 2009; 28: 3083-107

89. Yadeau JT, Liu SS, Rade MC, Marcello D, Liguori GA: Performance characteristics and validation of the Opioid-Related Symptom Distress Scale for evaluation of analgesic side effects after orthopedic surgery. Anesth Analg 2011; 113: 369-77

90. Gornall BF, Myles PS, Smith CL, Burke JA, Leslie K, Pereira MJ, Bost JE, Kluivers KB, Nilsson UG, Tanaka Y, Forbes A: Measurement of quality of recovery using the QoR-40: a quantitative systematic review. Br J Anaesth 2013; 111: 161-9

91. Spallone V, Morganti R, D'Amato C, Greco C, Cacciotti L, Marfia GA: Validation of DN4 as a screening tool for neuropathic pain in painful diabetic polyneuropathy. Diabet Med 2012; 29: 578-85