PART B
STUDY DESCRIPTION

TITLE OF PROTOCOL	Uniport and multiport epidural catheters in post-surgical patients		
Principal Investigator	Philip Hess		
Co-Investigators	Michael Foley, MD, Meghan Connolly , NP, Marc Shnider, MD		
Mailing Address	Department of Anesthesia, Critical Care and Pan Medicine, Beth Israel Deaconess Medical Center, Yamins 219, 330 Brookline Ave., Boston, MA 02215		
E-Mail Address	phess@bidmc.harvard.edu		
P.I.'s Telephone	7-3353	P.I.'s Pager 34467	Fax:7-4879
Sponsor/Funding Source	Beth Israel Anesthesia Foundation		

B1. PURPOSE OF PROTOCOL

Hypothesis:
We hypothesize that multi-port thoracic epidural catheters will provide superior pain relief when compared to uniport catheters for post-surgical patients.

B2. SIGNIFICANCE AND BACKGROUND FOR THE STUDY

Epidural analgesia (pain relief) is an effective treatment for post-surgical acute pain. The factors that determine the effectiveness of pain relief with epidural analgesia have been studied almost exclusively in the lumbar (low back) spaces for obstetrics (childbirth)[1,2,3,4]. These factors include the design of the epidural catheter, the type and dose of medications, and the volume of solution used. One of the important issues specific to the catheter design is whether the tip has a one end-hole, or multiple side holes. The number of holes has been suggested to affect the spread of epidural anesthetic over time, especially with low volume solutions. This has been demonstrated in older, stiffer epidural catheter designs, but has not been shown to be true with the newer, flexible epidural catheters.

The thoracic (upper back) epidural analgesia is widely employed for a many types of surgical pain. While the mechanism of pain relief is similar to that in the lumbar space, there may be differences between the two sites. Firstly, thoracic catheters tend to use low volume, high concentration medication solutions, which likely do not spread as effectively. Secondly, the thoracic catheters often need to be used for prolonged periods of time. Whereas the typical obstetric epidural is used for less than 12 hours, the post-surgical catheter is typically required for one to three days (or more). Finally, the thoracic space is narrow, with a thinner thecal sac, which might promote a difference in the spread of epidural solution.

Thoracic epidural analgesia is routinely used to control post-operative pain for a wide variety of surgical procedures. Based on the improved effectiveness of the one end-hole flexible epidural catheter in obstetrics, this design is commonly used in thoracic epidural analgesia. It has been observed that thoracic epidurals are somewhat less effective after a period of time when compared to the effectiveness of labor epidurals. This may be in part due to the inappropriate assumption that the

thoracic epidural space of a post-surgical patient is the same as the lumbar space of a parturient.

We seek to determine whether there is a difference in the analgesia provided by an FDA approved thoracic multi-port epidural catheter when compared to an FDA approved thoracic uniport epidural catheter as measured by pain scores, medication given for breakthrough pain, and need to add intravenous opioids. As mentioned previously, these catheters have been studied extensively in laboring patients but there is a striking paucity of literature regarding how anesthetic solutions spread in the thoracic epidural spaces of non-pregnant post-surgical patients and how this may be affected by catheter type. If the hypothesis is supported by results, it may change the practice within the study institution, and possibly, on a much larger scale. This study may also provide a foundation for further research into the physiology of the thoracic epidural space, how it differs from the lumbar epidural space, and how a medication solution spreads within this unique space.

References:

1. Spiegel, JE, Vasudevan, A, Li, Y, Hess, PE. "A randomized prospective study comparing two flexible epidural catheters for labour analgesia." *British Journal of Anaesthesia*. 103(3): 400-5. 2009.
2. D'Angelo, R, Foss, ML, Livesay, CH. "A Comparison of Multiport and Uniport Epidural Catheters in Laboring Patients." *Aneshthesia and Analgesia.* 84:1276-9. 1997.
3. Jaime, F, Mandell, GL, Vallejo, MC, Ramanathan, S. "Uniport Soft-tip, Open ended Catheters Versus Multiport Firm-tipped Close-ended Catheters for Epidural Labor Analgesia: A Quality Assurance Study. *Journal of Clinical Anesthesia.* 12:89-93. 2 200.
4. Grau, T, Leipold RW, Horter, J, Conradi, R, Martin, E, Motch, J. "The lumbar epidural space in pregnancy: visualization by ultrasonography." *British Journal of Anesthesia.* 86(6):798-804. 2001.

B3. DESCRIPTION OF RESEARCH PROTOCOL

A. Study Design – Overview, Methods, Procedures

This will be a double blind, prospective randomized trial to compare the effectiveness of uniport vs multiport thoracic epidural catheters. An investigator will approach patients who are to undergo a surgical procedure with a request for thoracic epidural analgesia. Inclusion criteria will include English speaking, surgery in the thorax or upper abdomen, age between 18 and 75, and expected use of epidural analgesia for >24 hours. Exclusion criteria will include contraindication to epidural catheterization, chronic use of opioids, chronic pain, allergy to the standard medications used for epidural pain relief, incarceration, Body Mass Index >40, delirium, dementia, or other mental status which would make follow-up impossible. All patients will receive informed written consent by an investigator.

After informed written consent is obtained, the patients will be randomized to receive either a flexible multiport catheter or a flexible uniport catheter in the thoracic space. The anesthesia team providing care to the subject will then place the epidural. The APS NP that will follow the subject post operatively will be blinded to the catheter type (these catheters look the same when in place). An appropriate epidural test dose will be used to confirm non-intravenous or intravascular placement. The patient will be assessed for a change in sensory level approximately 10 minutes after administration of test dose to ensure that the epidural catheter is in the epidural space. The epidural will then be taped in place per normal protocol such that the different epidural catheter types will not be identifiable (except for when the epidural is finally removed).

Intraoperative Management:
All epidural infusions will be started intraoperatively at a rate of 6 mL/hr of standard APS 10 epidural solution. The rate of the epidural intraoperatively will then be titrated from 6-12mL/hr at the discretion of the anesthesiologist performing the case. The epidural will not be shut off for hypotension unless the patient is persistently hypotensive despite adequate fluid resuscitation and vasopressor treatment.

Postoperative management:
All patients will receive a continuous infusion of APS 10 solution (includes bupivacaine and hydromorphone) at a rate between 6 and 12 ml per hour in the PACU. The postoperative nurse using current practice guidelines for all patients will adjust the postoperative infusion rate appropriately. Once the patient is comfortable with an appropriate epidural infusion, they will be transferred to the post-surgical floor.

In the event of uncontrolled pain the following protocol will be employed:

1. A sensory coverage level should be checked using ice. The epidural position and connections should also be verified.
2. If the provider believes the epidural is still appropriately placed the epidural should be bolused with 5 mL APS 10 assuming hemodynamic stability. If the patient is on the floor the epidural infusion rate can be increased by 5 -10 mL/hr for 1 hr then returned to the typical range. This may be repeated to give a second bolus.
3. If the practitioner believes that the catheter was placed too deep in the epidural space the catheter may be pulled back but should not be pulled back more than 2 cm from the

original position.
4. If the patient has a sensory level that isn't completely covering the area of pain consider increasing the rate of the infusion.
5. If the patient continues to have pain the patient may be started on IV/PO Acetaminophen if the patient has no contraindications to this drug.
6. Consider addition of NSAIDs and/or gabapentin.
7. If the patient continues to have inadequate pain control refractory to the above then one can consider splitting the epidural (adding an enteral or IV Opioid).

Assessments:
The primary outcome of the study will be the incidence of failed epidural analgesia, defined as the need to add intravenous opioids or halting or replacing the epidural catheter because of lack of pain control. Other outcomes that will be measured include the incidence of supplemental treatments, the required dose of medication (hourly average), need for treatment of side effects, and complications.

All patients will be assessed for pain using an 11-point visual analogue scale. Sensory level will be recorded daily as will any episodes of breakthrough pain. Sensory level will be assessed with a change in perception to ice. All assessments will be performed preoperatively, in the PACU (when the patient is deemed to be awake, alert and responding appropriately), and on each subsequent postoperative day until the catheter is removed per the standard nursing epidural policy.

B. Statistical Considerations

Sample Size Justification: Based on the expected differences in efficacy, power analysis was performed (PS software, Vanderbilt University) using alpha=0.05, β=0.80 and incidence of epidural failure (primary endpoint) difference of 20% (no current studies, estimated from previous experience), we estimate that 91 patients would be needed per group. We would plan to enroll 120 patients per group (240 patients total) to account for drop out due to epidural catheter misplacement, accidental dislodging, or halting of the epidural due to side effects, such as low blood pressure. Drop out rate should be minimal given that all of these patients will be inpatients on surgical wards that will not require post-discharge follow up.

Data Analysis: All continuous data (e.g. secondary endpoints of pain scores) will be assessed for normality using the Shapiro-Wilke test. Comparisons between the primary outcome (epidural failure) will be performed using Fisher's exact test (or chi square depending on effect size). Time to epidural failure for each catheter will be plotted on a failure vs time curve (like a survival curve). Comparison of other outcomes will be performed using the t-test, Mann-Whitney test, Fisher's exact, as appropriate. Duration of epidural analgesia (time to halting) will be analyzed using log-rank analysis. Finally, we will perform a logistic regression to attempt to determine factors that may be associated with epidural analgesia failure. The data will be stored electronically on secure BIDMC servers behind the firewall. The computations will be done using STATA and/or SPSS. The above plan was made in conjunction with biostatistician Roger Davis, SCD.

C. Subject Selection

Selection: Patients who are to undergo a surgical procedure with a request for thoracic epidural analgesia will be approached by an investigator. Additionally, the acute pain resident and/or nurse practitioner will look through the daily OR schedule to identify patients that may benefit from thoracic epidurals and discuss with the primary anesthesia team whether this is included in their anesthetic plan. Inclusion criteria will include English speaking, surgery in the thorax or upper abdomen, age between 18 and 75, and expected use of epidural analgesia for >24 hours. We are expecting the racial, ethnic and gender composition of our sample to be representative of the typical BIDMC Boston campus aggregate patient population. Exclusion criteria will include contraindication to epidural catheterization, chronic use of opioids, chronic pain, allergy to the standard medications used for epidural pain relief, incarceration, Body Mass Index >40, delirium, dementia, or other mental status which would preclude providing own informed consent. Women of childbearing age will not be excluded from this study. All patients would receive informed written consent by an investigator.

B4. POSSIBLE BENEFITS

Benefits: Possible benefits include improved pain control following extensive surgical procedures involving the thorax and/or upper abdomen. Our belief is that the smaller/thinner thoracic epidural space will be disproportionally affected by a slightly misplaced end hole (uniport) epidural catheter and that there is a real possibility that the spread of anesthetic solution from a multiport epidural catheter will be superior. If we demonstrate that multiport catheters are superior in our study group this would very likely change standard of care from uniport catheters to using multiport epidural catheters for thoracic epidural analgesia not only at our institution but hopefully on a much larger scale (nation and world wide). Given the many thousands of thoracic epidurals placed annually in the U.S. a 20% (what we're predicting) improvement in analgesia could provide profoundly better pain relief to future post-surgical patients.

B5. POSSIBLE RISKS AND ANALYSIS OF RISK/BENEFIT RATIO

We believe the primary risks should be identical to the risks for any thoracic epidural. We do not believe that any of our patients will be at any increased risk from receiving a multiport catheter when compared to receiving a uniport catheter (or vice versa). Thus, we believe this to be a minimal risk intervention. We do not anticipate any risks above what patients already have for our current thoracic epidural analgesia procedures. These risks include, but are not limited to, bleeding, infection, post dural puncture headache (when dura accidentally penetrated – happens in about 1% of epidural placements). Risks of any nerve injury or spinal cord injury are extremely rare (probably less than 1:50,000).

Should any of the participants experience any of the above side effects they would be offered, as always, appropriate treatment such as an epidural blood patch for inadvertent dural puncture. Should any participants experience any unexpected psychological effects we would ask our Psychiatric

colleagues to see the patient in addition to providing extensive support and empathy.

Given the possibility of significantly increased pain control in post-surgical patients and the low risk of this intervention we believe that benefit significantly outweighs the risk.

B6. RECRUITMENT AND CONSENT PROCEDURES

Recruitment

Generally, the anesthesia team providing care to the patient (not the acute pain team which will be consulted post-operatively to manage the epidural) will determine whether the patient will benefit from post-operative epidural analgesia. Patients who are to undergo a surgical procedure with a request for thoracic epidural analgesia will be approached by an investigator. Inclusion criteria will include English speaking, surgery in the thorax or upper abdomen, age between 18 and 75, and expected use of epidural analgesia for >24 hours. Exclusion criteria include contraindication to epidural catheterization, chronic use of opioids, chronic pain, allergy to the standard medications used for epidural pain relief, incarceration, Body Mass Index >40, delirium, dementia, or other mental status which would make follow-up impossible. All patients would receive informed written consent by an investigator.

Consent

Both verbal and written consent will be obtained directly from the patient. Consent will be obtained after the patient has been consented by the primary team for general anesthesia and epidural analgesia. The consent for the study will take place in the holding area, in a private setting, prior to administration of any sedatives/anxiolytics. We do not feel that it will be possible to obtain consent/thoroughly discuss the study with prospective patients prior to the day of surgery given the complex nature of the decision by the primary anesthesia team to place a thoracic epidural (many patients who are eligible inevitably don't receive thoracic epidurals for a wide variety of reasons). Risks, benefits, alternatives and lack of penalty for opting out will all be thoroughly discussed. Our written consent form has been drafted and is included in this application.

Subject Protection

No vulnerable subjects have been identified for this study. However, patients undergoing the types of procedures that require post-operative thoracic epidural analgesia tend to be patients with significant disease (i.e. Whipple for pancreatic cancer, thoracotomy for lung cancer). Patients who cannot consent for themselves will be excluded from the study because they may not reliably be able to communicate pain scores and other subjective measures.

B7. STUDY LOCATION

Privacy

Patients will be screened in a private area in the pre-op holding area. Once enrolled the study specifics and consent will be placed in the confidential patient chart. All patient data will be collected and maintained on secure BIDMC servers behind the firewall. No follow up will be necessary following removal of the epidural and discharge from the hospital.

Physical Setting

This study will take place in the pre-op holding area, the post anesthesia care unit and the patient's room. All of these locations have the ability to create a private space to confidentially discuss patient information. No further clinical follow up will be necessary following discharge from the hospital.

B8. DATA SECURITY

All data will be kept electronically on the BIDMC servers behind the firewall. No data will be stored on local hard drives of personal computers, tablets or smart phones. All paper data will be secured in the confidential paper chart or secured in the locked anesthesia office.

B9 Multi-Site Studies

Is the BIDMC the coordinating site or is the BIDMC PI the lead investigator of the multi-site study?
☐ Yes ☒ No

B10 Dissemination of Research Results

All patients will queried as to whether they would like the final results of the study. Those who indicate they would like results will receive an email when results are available. All patients will receive a written thank you from the investigators following completion of the study.