TITLE: Traditional loss-of-resistance technique vs Compuflo-aided technology for placement of a thoracic epidural catheter: a randomized trial of the effect on the success rate

NCT Number: 03826186

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Form Content

I. Project Introduction

I.1 *Project to be reviewed by:*
IRB-01

I.2 *Project Title:*
Traditional loss-of-resistance technique vs Compuflo-aided technology for placement of a thoracic epidural catheter: a randomized trial of the effect on the success rate

I.3 *Short Title (optional):*
Compuflo epidural study

I.4 *Provide a short summary of the purpose and procedures of the study proposed in this IRB application.*

- *DO NOT include information on studies not proposed in this application.*
- *Use LAY terminology only. This must be easily understandable by IRB community members and nonscientists.*
- *DO NOT cut and paste technical abstracts from funding applications that may not be understood by a general audience.*

Traditionally, loss-of-resistance (LOR) to air or saline with a special ground-glass syringe is the technique used to identify epidural space, but failure rates up to 30% have been reported using this technique for thoracic epidural placement. This failure rate has sparked the search for newer techniques to improve the success rate for placement.The CompuFlo epidural system is a device that provides anesthesiologists and other healthcare providers the ability to quantitatively determine and document the pressure at the needle tip in real time.
The device's proprietary dynamic pressure sensing technology (DPS) allows it to provide objective visual and audible in-tissue pressure feedback that allows anesthesiologists to identify the epidural space. The purpose this research study is to compare the success rate of the two different approaches (traditional method v/s CompuFlo assisted) to thoracic epidural placement.

The device (CompuFlo) is currently FDA approved for use with Lumbar epidurals and not for Thoracic epidurals. We believe that the device does not pose a significant risk if used for thoracic epidurals and the explanation is presented below (Originally I planned to include this explanation in Section VII.B.31 - However, I could not include it because of the word count. I was asked to include it here after discussion with a HawkIRB team member over the phone)

Several factors should be taken into consideration when assessing the potential risks associated with the use of Compuflo for thoracic epidural catheter placement. An understanding of the principles underlying placement of epidural catheters using the traditional technique and how Compuflo complements the traditional technique, as well an understanding of the neurological risks associated with thoracic and lumbar epidural catheter placement, is helpful. Finally, an appreciation of the differences and similarities in approaches to identifying thoracic and lumbar epidural spaces is useful.

Traditional technique vs Compuflo use: Using the traditional technique (loss-of-resistance technique), the epidural needle is advanced through the subcutaneous tissues with the needle stylet in place until the needle tip is positioned in the interspinous ligament—this is noted by the proceduralist by an increase in tissue resistance (attempted injection into ligamentous tissue is met with high resistance). The stylet or introducer is removed, and a ground-glass syringe filled with 2-3 ml of saline with an air bubble is attached to the hub of the epidural needle. If the tip of the needle is within the ligament, gentle attempts at injection are met with resistance, and injection of the saline is not possible. The needle is then slowly advanced, millimeter by millimeter, with either continuous or rapidly repeating attempts at injection. As the tip of the needle enters the posterior epidural space, a sudden loss of resistance is noted, and the saline injects easily. Once the needle tip is in the epidural space, the epidural catheter is threaded through the needle and the needle is removed, leaving the catheter sited in the epidural space. The Compuflo technique complements this basic technique. Similar to the traditional technique, the needle is advanced through the subcutaneous tissues with the stylet in place until the interspinous ligament is entered, as noted by an increase in tissue resistance. After removing the stylet, flexible tubing from the Compuflo disposable tubing-syringe set is attached to the hub of the needle instead of the traditional ground-glass syringe. The fluid-filled syringe is placed in the Compuflo device. The needle is then advanced continuously with the device electronically sensing pressure in real time, providing a numerical value (100 to 150 mm Hg) on the read-out screen. As the tip of the needle enters the posterior epidural space, a sudden loss of resistance (associated with a significant loss of pressure to less than 50 mm Hg) is noted. An audio signal also signals the acute change in pressure. Essentially, the Compuflo is a sophisticated means of assessing loss-of-resistance. In contrast to the traditional technique, in which a subjective tactile response indicates needle-tip entry into the epidural space, the loss-of-resistance signal achieved with Compuflo is objective. The device has been approved by FDA to assist with lumbar epidural catheter placement. The loss-of-resistance technique for identifying the lumbar epidural space is essentially the same as that used for identifying the thoracic epidural space.

Neurological risks associated with epidural catheters – lumbar vs thoracic: Lumbar epidural catheters are usually placed below the level (L3-4 or L4-5) where the spinal cord ends (L1). In contrast, thoracic epidural catheters are placed at a level where the spinal cord is deep to the epidural space. If unintentional dural puncture occurs, the epidural needle may come in contact with the thoracic spinal cord. Under usual circumstances, the dura-arachnoid mater is not punctured during placement of an epidural catheter. A known complication of epidural catheter placement is the unintentional puncture of the dura-arachnoid mater–the epidural needle passes through the posterior epidural space because the proceduralist does not recognize that the tip is located in the epidural space and thus continues needle advancement. Rarely, there may be anatomically abnormalities that contribute to unintentional dural puncture. The risk of unintentional dural puncture during placement of lumbar epidural catheters is estimated to be 1% (0.19% to 3.6%). The incidence of dural perforation after thoracic epidurals is similar to or even smaller than that reported in the lumbar region (0.42% -1.2%). In general, thoracic epidural catheterization does not appear to be associated with more complications or more serious complications than reported in the literature for lumbar epidural catheterization. In fact, no permanent nerve injuries related to thoracic epidural catheterization were observed in a study which included more than 4,000 patients having abdominal or abdominothoracic surgery, and the predicted maximum risk for permanent neurologic complications, using the upper bounds of the 95% confidence interval, is 0.07%.

Needle approach to the epidural space--lumbar vs thoracic: Because the Compuflo device is currently approved for lumbar epidural, but not for thoracic epidural catheter insertion, it is important to understand the differences and similarities in approaches to identifying thoracic and lumbar epidural spaces. Difference: In general, two approaches exist to for needle advancement from the dorsal skin surface to the epidural space – midline or paramedian. With the midline approach, the needle entry is along the midline sagittal plane (as suggested by the name), between the spinous processes of adjacent vertebrae. With the paramedian approach, the needle entry is through a point approximately 1-cm lateral to midline and the needle is angled medially with the goal of entering the epidural space in the midline. Most lumbar epidural catheters are placed using the midline approach—the spinous processes extend at an approximate right angle from the vertebral bodies, making needle advancement between two adjacent spinous processes relatively easy. However, in the mid- and high-thoracic regions, the spinous processes are angled downward at an extreme angle, making the midline approach between the spinous processes much more difficult. The paramedian approach is therefore preferred for placing thoracic epidural catheters. Similarity: The principle behind identification of the epidural space using 'loss-of-resistance' to saline injection is the same, whether a midline approach or a paramedian approach is used. The resistance to injection decreases precipitously once the epidural needle tip exits the ligamentous tissue and enters the posterior epidural space.

To summarize, in the proposed study we will use Compuflo to facilitate thoracic epidural catheter placements in the study group. The ground-glass syringe used for the loss-of-resistance technique will be replaced by the Compuflo device to identify the epidural space. Given that the device has been shown to effectively identify the lumbar epidural space with no increase in complications compared to the traditional technique, we feel that the risks of using this device to identify the thoracic epidural space which relies on the same 'loss-of-resistance' technique, will be no different than the traditional method. Moreover, the device may actually decrease the risks associated with epidural catheter placement—the risk of unintentional dural punctures may be lower because proceduralists will be provided with objective data.

I.5 ***Specify your research question(s), study aims or hypotheses (do not indicate "see protocol")***

Primary research question to be answered: Does use of the Compuflo technology improve the success rate of thoracic epidural analgesia?

We hypothesize that the use of Compuflo to identify the thoracic epidural space during catheter placement for postoperative analgesia will increase the success rate of thoracic epidural catheter placement from 75% to 90%

What are the secondary question(s):
1. Characterize the Compuflo waveforms observed during identification of the thoracic epidural space?
2. Utilization of Compuflo to record pressure readings from the epidural space followed by analysis of epidural pressure waveform patterns to see if particular patterns associate with better success rate?
3. Are there differences in safety and complication outcomes between the two techniques (e.g. unintentional dural puncture, time for procedure, postoperative outcomes)?

I.6 ***Background and significance and/or Preliminary studies related to this project. (do not indicate "see protocol")***

Epidural analgesia (EA) is commonly utilized for patients undergoing thoracic and abdominal surgery. The benefits of epidural analgesia include decreased opioid consumption, improved pulmonary function, decreased postoperative ileus and increased patient satisfaction with pain control(1-3). Historically, a loss of resistance (LOR) technique has been used to locate the epidural space, but failure rates up to 30% have been reported using this technique for epidural placement. In recent studies where trainees (which will happen in our study) performed most of the thoracic epidural blocks, the following failure rates were reported with conventional technique:
P Leurcharusmee, Tran etal 23.1% (4)
M Parra etal 26% (5)
M Gist etal: 16% (7)

Several other methods (4-7), have been employed to improve success rate of thoracic epidural placement including: 1) Fluoroscopic guidance for placement of thoracic epidurals 2) Loss of resistance in combination with nerve stimulation 2) Epidural waveform analysis in combination with loss of resistance. All these methods have been able to decrease the failure rate to less than 5%. However, they are not routinely used out side of the study settings because of practical difficulties. Compuflo technology provides additional information (objective end points) when the epidural is placed in a way very similar to the conventional technique which we believe can improve our success rates. The device is FDA approved for lumbar epidural placement and since the principle behind placement of thoracic epidural (LOR technique) is similar; this device should be helpful in placement of thoracic epidurals.
Given the tangible improvements in postoperative outcomes (decreased ileus, decreased opioid consumption, increased patient

No

III.5 *What is the current status of this funding source?*

Source	Status	Other Status Description
Milestone Scientific	Awarded	

IV. Project Type

IV.1 *Do you want the IRB to give this project*
Regular (expedited or full board) review

IV.2 *Enter the date you will be ready to begin screening subjects/collecting data for this project. (If you do not have a specified date, add "upon IRB approval")*
01/02/2019

IV.3 *Are you requesting a waiver of informed consent/authorization (subjects will not be given any oral or written information about the study)?*
No

V. Other Committee Review

V.1 *Does this project involve any substance ingested, injected, or applied to the body?*

- *Do not answer yes, if the involvement includes a device, wire, or instrument*

Yes

V.1.a *What is/are the substance(s):*
The substance used is lidocaine with epinephrine.

The same substance is used in routine clinical practice for testing epidural catheter placement.

In this study, the quantity used is higher (additional test dose is given). The higher dose is required to test the loss of temperature sense following epidural placement which is not done in routine clinical practice.

V.1.b *Are any of these substances defined as a Schedule I - V Controlled Substance?*
No

V.2 *Are any contrast agents used for any purpose in this study?*
No

V.4 *Are all drugs or substances in this study being used within the FDA approved population (i.e., children, adults)?*
Yes

V.5 *Are all drugs or substances in this study being used within the FDA approved indication (i.e., disease, condition)?*
Yes

V.6 *Are all drugs or substances in this study being used within the FDA approved dose?*
Yes

V.7 *Are all drugs or substances in this study being used within the FDA approved route of administration?*
Yes

V.9 *Will any subject be asked to undergo a diagnostic radiation procedure (including radiographic, nuclear medicine, DEXA)?*
No

V.14 *Will any subject be asked to undergo a radiation therapy procedure (including external beam therapy, brachytherapy, or nuclear medicine therapy)?*
No

V.20 *Does this project involve the deliberate transfer of recombinant or synthetic nucleic acid molecules, or DNA or RNA derived from recombinant or synthetic nucleic acid molecules, into one or more human research participant?*
No

V.21 *Will any portion of this project be conducted in the CRU, or does it use any CRU resources?*
No

V.22 *Will this project use:*

- *any resource/patients of the Holden Comprehensive Cancer Center*
- *involve treatment, detection, supportive care, or prevention of cancer*

No

V.25.a *Will the study involve <u>any</u> of the following activity at UI Health Care, even if subjects or their insurance will not be billed for the item or service, and regardless of the study funding source (including studies with departmental or no funding)?*

- *Procedures, tests, examinations, hospitalizations, use of Pathology services, use of clinic facilities or clinical equipment, or any patient care services, including services conducted in the Clinical Research Unit; or*
- *Physician services or services provided by non-physicians who are credentialed to bill (ARNPs, Physician Assistants, etc.)*

Yes

V.25.b *Will there be any procedures or services that may happen as part of a subject's regular medical care and as part of the study?*
Yes

V.25.c *Will any study equipment or devices be supplied by a study sponsor?*
Yes

V.25.d *Please describe the equipment or device(s) being provided and what it will be used for*
The device used in this study is called Compuflo Epidural, a product of Milestone Scientific, Livingston, NJ. CompuFlo Epidural's pressure sensing technology provides an objective tool to consistently and accurately identify the epidural space. Currently, the device is FDA approved for use in assisting with placement of Lumbar epidurals. This study involves placement of Thoracic epidurals which will be considered as an off-label use as it is not approved for this indication.

Milestone Scientific will provide the equipment and the disposables used in this investigation.
Departmental resources will be utilized for all other funding needed in this study.
The investigators will retain full control of the investigation, including study design, protocol implementation, data analysis, and results interpretation.

V.25.e *Is there or will there be an internal budget for this study?*
Yes

V.25.f *Is there or will there be an external budget for this study?*
No

V.26 *The study involves Department of Nursing Services and Patient Care nursing, nursing resources or evaluates nursing practices at UI Health Care.*
No

VI. Subjects

VI.1 *How many adult subjects do you expect to consent or enroll for this project?*
133

VI.2 *What is the age of the youngest adult subject?*
18.0

VI.3 *What is the age of the oldest adult subject?*
75.0

VI.4 *What is the percentage of adult male subjects?*
50

VI.5 *What is the percentage of adult female subjects?*
50

VI.6 *How many minor subjects do you expect to consent or enroll for this project?*
0

VI.13 *Describe EACH of your subject populations*

- *Include description of any control group(s)*
- *Specify the Inclusion/Exclusion criteria for EACH group*

Subject population will include patients scheduled for thoracic epidural anesthesia at the University of Iowa Hospitals and Clinics.

Inclusion Criteria
-Age 18 years to 75 years
-BMI 18-50 kg/m2

Exclusion Criteria
- Contraindication to thoracic epidural anesthesia
- Allergy or hypersensitivity to local anesthetics
- Patients unable to provide written informed consent
- Pregnant women and prisoners
- Patients in whom a epidural test dose of 5 ml is contraindicated, eg, valvular heart disease

VI.14 ***Provide an estimate of the total number of subjects that would be eligible for inclusion in each of your study populations (include your control population if applicable)***
The Acute Pain Service at the University of Iowa Hospitals and Clinics places 600 to 700 Thoracic epidurals in a year. Of those at least 75-80% of patients meet inclusion criteria for the study.

VI.15 ***Describe how you will have access to each of your study populations in sufficient number to meet your recruitment goals.***
Based on a 40-50% study patient enrollment from about 600-700 patients receiving thoracic epidurals, We plan to have the study patients enrolled in about 12-18 months. I am an anesthesiologist with fellowship training in Regional Anesthesia and Acute Pain Medicine. These are the types of patients that I take care of on a daily basis for my current practice. Once, the study is approved from IRB, I and the other faculty members on Acute Pain Service will be involved in patient recruitment and in performing the essential regional anesthesia procedures necessary for this study.

VI.16 ***Do you plan to recruit/enroll non-English speaking people?***
No

VI.18 ***Do you propose to enroll any of the following in this study as subjects?***

- ***Employee of the PI or employee of a research team member***
- ***Individual supervised by PI or supervised by member of research team***
- ***Individual subordinate to the PI or subordinate to any member of the research team***
- ***Student or trainee under the direction of the PI or under the direction of a member of the research team***

No

VI.20 ***Will subjects provide any information about their relatives?***
No

VI.23 ***Will anyone (other than the subject) provide you with information about the subject (e.g. proxy interviews)?***
No

VI.26 ***Is this project about pregnant women?***
No

VI.27 ***Will this project involve fetuses?***
No

VI.28 ***Does this project involve adult subjects who may be incompetent or have limited decision-making capacity on initial enrollment into the study?***
No

VI.32 ***Does this project involve subjects whose capacity to consent may change over the course of the study?***
No

VI.37 ***Does this project involve prisoners as subjects?***
No

VII.A. Project Description (A)

VII.A.1 ***Where will project procedures take place (check all that apply)?***
- UIHC - Main Operating Room, Intensive Care Units

VII.A.2 ***Is this project also being conducted by other researchers at their own sites (e.g. a multi-site collaborative project)?***
No

VII.B. Project Description (B)

VII.B.1. *Does this project involve any of the following (Check all that apply):*

- [x] **Interventional** – Includes **Clinical (or Treatment) trial, Physiology intervention/study, Behavioral intervention/study, Diagnostic Trial.**
  - [x] **Clinical (or Treatment) trial** – A prospective biomedical or behavioral research study of new treatments, new drug or combinations of drugs, new devices, or new approaches to surgery or radiation therapy. (NIH and ClinicalTrials.gov & FDA)
  - [ ] **Physiology intervention/study** – A pharmacologic or measurement study aimed at understanding basic mechanisms of disease and/or of normal human physiology, often without any therapeutic intent (though a clinical trial could include such components, often labeled as "translational" or "basic science" aims.) Measurements in such studies could include, but are not limited to, a blood draw, EKG, EEG, MRI, auditory or sensory testing, checking vital signs, DEXA scans, eye tracking, specimen collection, exercise, fasting, special diets, etc.
  - [ ] **Behavioral intervention/study** – May be used to refer to studies of individual or group behavior. This option does not include drugs, biologics, or devices but could include psychotherapy, lifestyle counseling, behavior modification, etc.
  - [ ] **Diagnostic trial** – Protocol designed to evaluate one or more interventions aimed at identifying a disease or health condition (ClinicalTrials.gov & FDA)
- [ ] **Observational**
- [ ] **Expanded Access** – A process regulated by the Food and Drug Administration (FDA) that allows manufacturers to provide investigational new drugs to patients with serious diseases or conditions who cannot participate in a clinical trial. Examples of expanded access include non-protocol access to experimental treatments, including protocol exception, single-patient IND, treatment IND, compassionate use, emergency use, continued access to investigational drug, and parallel track (ClinicalTrials.gov & FDA).
- [ ] **Registry** – The collection and maintenance of data (not including biologic samples) in which: (1) the individuals in the registry have a common or related condition(s), and/or (2) the individuals in the registry are interested in being contacted for future studies by investigators other than those listed in Section II of this project.(UI Guide)
- [ ] **Repository** – The collection, storage, and distribution of human biologic samples and/or data materials for research purposes. Repository activities involve three components: (i) the collection of data and/or specimens such as blood, tissue, saliva, etc.; (ii) the storage of data or specimens, and data management function; and (iii) the sharing of data/specimens with recipient investigators other than the original investigators. (paraphrased from OHRP)
- [ ] **Other**

VII.B.1.a *Does this project involve any of the following (Check all that apply):*

- [ ] **Phase I trials** – include initial studies to determine the metabolism and pharmacologic actions of drugs in humans, the side effects associated with increasing doses, and to gain early evidence of effectiveness; may include healthy participants and/or patients (ClinicalTrials.gov & FDA)
- [ ] **Phase II trials** – include controlled clinical studies conducted to evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study and to determine the common short-term side effects and risks(ClinicalTrials.gov & FDA)
- [ ] **Phase III trials** – include expanded controlled and uncontrolled trials after preliminary evidence suggesting effectiveness of the drug has been obtained, and are intended to gather additional information to evaluate the overall benefit-risk relationship of the drug and provide an adequate basis for physician labeling(ClinicalTrials.gov & FDA)
- [x] **Phase IV trials** – studies of FDA-approved drugs to delineate additional information including the drug's risks, benefits, and optimal use(ClinicalTrials.gov & FDA)

VII.B.2 *Does this project involve a drug washout (asking subject to stop taking any drugs s/he is currently taking)?*
No

VII.B.6 *Will any subjects receive a placebo in this study when, if they were not participating, they could be receiving an FDA-approved treatment for their condition?*
No

VII.B.11 *Is there a separate, written protocol that will be submitted in addition to this IRB New Project form? (Note: a grant application is not considered to be a protocol)*
No

VII.B.18 *Does this project involve testing the safety and/or efficacy of a medical device?*
Yes

VII.B.19 *Describe in detail procedures in place for maintaining device shipment and receipt records:*
MOR Workroom Supervisor, will maintain device shipment/receipt records.

VII.B.20 *Who will be responsible for maintaining these shipment and receipt records?*
MOR Workroom Supervisor, will maintain device shipment/receipt records.

VII.B.21 *Describe in detail procedures in place for tracking use and disposition of devices described in this study:*
The study involves use of 'CompuFlo Epidural' - A device designed to aid with epidural placement.
The device has been leased to the Department of Anesthesia.

There will be disposables (single use) which are supplied to the Anesthesia work room by the company.
The company will supply these disposables free of cost for the study.
Disposables including syringe, pressure transducer and some wires which connect to the device will be discarded appropriately in the block area after use.

VII.B.22 *Who will be responsible for maintaining these use and disposition tracking records?*
MOR Workroom Supervisor, will maintain device tracking records.

VII.B.23 *Describe in detail procedures in place to limit access to authorized study personnel for the storage, control, and dispensing of the investigational devices. (For example, investigational devices are kept in a locked area away from approved devices or have a keyed interlock, and only study personnel authorized to dispense the device have the keys)*
The device will have a RESEARCH USE ONLY tag on the machine & study personnel will only be authorized to use the device. It will be kept in the MOR - Acute Pain Service area, where staff members of Acute Pain Service will be responsible for its use.

VII.B.24 *Is the device FDA-approved for the way it will be used in this study?*
No

VII.B.25 *Is there an IDE (Investigational Device Exemption) for this device in this research project?*
No

VII.B.29 *Indicate the appropriate FDA status you and/or the sponsor are requesting for the use of this device in this study.*
Non-Significant Risk (NSR) device/software

VII.B.31 *Provide a detailed rationale for why this device meets the FDA definition of a Non-Significant Risk Device (NSR)*
21 CFR 812.3 defines a Significant Risk device as an investigational device that:
1.Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;
2.Is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;
3.Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or
4.Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject

The device used in this study does not fall into any of the above categories.

The device used in this study will help to improve the success rate of epidural placement there by helping with better pain management.
The device (CompuFlo) is currently FDA approved for use with Lumbar epidurals and not for Thoracic epidurals. We believe that the device does not pose a significant risk if used for thoracic epidurals and the explanation is presented in Section I.4.

VII.B.32 *Provide a summary of prior investigations with this device.*
A.Prior investigations performed with this device mostly involve its use in lumbar epidural placement:

1.CompuFlo® Assessment Study (COMPASS): A Randomized, Controlled, Parallel Group, Multicenter, Pivotal Study to Assess the Safety and Effectiveness of the Epidural Space Verification With the CompuFlo® Epidural Computer Controlled System

https://clinicaltrials.gov/ct2/show/NCT02378727.
This study was performed in multiple centers across the US and primarily looked at the success rate of lumbar epidurals with this device.
This study formed the basis for FDA approval of this device for lumbar epidural as per a press release on their website:
https://ir.milestonescientific.com/press-releases/detail/234/milestone-scientific-announces-510k-fda-clearance-for

2. A pilot study was conducted at the University of Texas to identify lumbar epidural space using this device. The results were published in 'Regional Anesthesia Pain Medicine' - a leading journal for the field. 'Identification of the epidural space using pressure measurement with the compuflo injection pump--a pilot study' - This investigation demonstrates that a computerized injection pump can be used to identify the epidural space and can serve as a base for further comparative research to determine whether this technology can increase the success rate of EA or lower the incidence of side effects.
https://www.ncbi.nlm.nih.gov/pubmed/18675746

3.Another study done in obstetric patients for lumbar epidurals - "Experimental validation of the CompuFlo® epidural controlled system to identify the epidural space and its clinical use in difficult obstetric cases" - CompuFlo was validated as a tool to identify the epidural space. It may also assist trainees in successful

epidural placement in difficult cases.
https://www.ncbi.nlm.nih.gov/pubmed/29914784

B.There is only study currently looking at it's use in thoracic epidurals (Details are listed in next section). We believe that more and more people will start studying the device in the near future for use in thoracic epidurals.

VII.B.33 *Have there been any prior IRB reviews (at UI or elsewhere) and/or determinations made with regard to this device?*
Yes

VII.B.34 *Provide a discussion of these reviews/determinations.*
Univ of Miami has approved a pilot study regarding thoracic epidural
https://clinicaltrials.gov/ct2/show/NCT03376256

The Univ of Texas IRB had approved the study for lumbar epidurals that was conducted at UT and this formed the publication of Ghelber, et.al.
https://www.ncbi.nlm.nih.gov/pubmed/18675746

These are the details which we could collect online as well as from the Company (Milestone Scientific)

VII.B.35 *Has the FDA made an assessment of risk with regard to this device?*
Yes

VII.B.36 *Has this device/software been approved by the FDA for another indication or in another form from its use in this project?*
Yes

VII.B.37 *Describe differences between approved device/software and its use in this study:*
There will be no difference between the approved device/software and the way it will be used during this study.
Device/Software will essentially remain the same.
The device will be used for thoracic epidurals (not approved) instead of lumbar epidurals (approved use).

VII.C. Project Description (C)

VII.C.1 *Does this project involve any research on genes or genetic testing/research?*
No

VII.D. Project Description (D)

VII.D.1 *Check all materials/methods that will be used in recruiting subjects (you will need to attach copies of all materials at the end of the application):*

- Advertisements -
- Website - https://uihc.org/clinicaltrials/studies Some subjects may be identified from responses to the Iowa Clinical Research & Trials website
- Use of any information available to the researchers or their colleagues because this person is a patient OR use of any information considered to be Protected Health Information (PHI) OR review of patient/clinic records - Patients scheduled for thoracic epidurals for postop analgesia in the main operating room will be screened prior to determine if they are eligible to participate in the study. Records in EPIC will be looked at to determine if they meet the inclusion and do not meet the exclusion criteria. Patients in the ICU or floor who get thoracic epidurals for analgesia will be screened in a similar way.

VII.D.2 *List the individual data elements you will need to access/use from the patient or clinic records to identify potential subjects for recruitment*
We will screen from the Operating room schedule and look at age, health status, present and past medical history, laboratory values, weight and medication lists. We will also screen from the prior anesthesia history to determine if each patient meets the inclusion criteria and has no criteria which would exclude the patient from the study.
The Acute Pain Service is consulted as part of routine workflow in case of patients needing thoracic epidurals outside of the operating room. Similar screening will be done for these patients to assess their eligibility for the study.

VII.D.3 *Describe why you could not practicably recruit subjects without access to and use of the information described above*
Our inclusion and exclusion criteria is based on age and health factors. We need to review these factors before approaching the patients.
We will be recruiting patients in the Main OR DOSA pre-operative holding area or patient care unit (ICU inpatient rooms on unit) in a private room with the door closed. It is essential to identify patients that appear to meet our inclusion criteria that can be approached to participate in our study. Our inclusion and exclusion criteria is based on age and health factors that can not be gained by just looking at the operating schedule.

VII.D.4 *Describe why you could not practicably obtain authorization from potential subjects to review their patient or clinic records*

for recruitment purposes.
We would not know who might be going into surgery/needing a epidural block without reviewing their medical records first.

VII.D.5 *Describe plans to protect the identifiers from improper use or disclosure*
All potential subjects whose charts are reviewed and excluded, will not have paper documentation recorded for the study. Any surgery schedules and information of potential subjects will be kept in a locked cabinet in a locked office within the Anesthesia dept. Any notes taken or schedules taken will be destroyed as soon as they are no longer needed, or sooner if necessary, in the hospital patient confidentiality shred bins. There will not be a list of all potential patients kept for future reference.

VII.D.6 *Describe plans to destroy identifiers at the earliest opportunity consistent with conduct of the research*
The printed information will be destroyed at the earliest opportunity in the hospital shred bins.

VII.D.7 *Does the research team agree that the requested information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the study, or for other research for which the use or disclosure of the requested information would be permitted by the HIPAA Privacy Rule*
Yes

VII.D.8 *Will a member of the research team discuss the study with the subject in person prior to the subject agreeing to participate?*
Yes

VII.D.9 *Describe the physical location where the consent process will take place:*
UIHC MAIN OR/DOSA area or In-patient floor/ICU patient unit - in a private room with the door closed/curtain pulled for privacy.

VII.D.10 *Will a member of the research team discuss the study with the subject by phone prior to the subject agreeing to participate?*
No

VII.D.12 *Who will be involved in the consent process (including review of consent document, answering subjects' questions)?*

VII.D.15 *Check all materials that will be used to obtain/document informed consent:*
- Consent Document

VII.D.16 *Are you requesting a waiver of documentation of consent (either no subject signature or no written document)?*
No

VII.D.19 *Before the subject gives consent to participate are there any screening questions that you need to directly ask the potential subject to determine eligibility for the study?*
Yes

VII.D.20 *List any screening questions you will directly ask the potential subject to determine eligibility.*
a) Will you be able to participate in a nerve block procedure- Epidural placement, where a needle is placed on your back to help with pain after surgery or trauma (for rib fracture patients)?
b) Do you have any numbness or tingling of the extremities?
c) Do you have any known spine problems?
d) Do you have any known liver disease?
e) Do you have any know kidney disease, excluding kidney stones?
f) Are you pregnant or think you may be pregnant?
g) Do you take any blood thinners?
h) Do you have any heart problems?

These are questions which are asked routinely in a patient getting epidural as part of their standard care.

VII.D.21 *Will you keep a screening log or other record that would include information on people who do not enroll in the study?*
Yes

VII.D.22 *Describe the information being collected and the purpose for keeping this information.*

'Reason for refusal' will be documented for otherwise eligible patients who decline participation.
We would like to know if the reason for refusal was due to the 'study part' or because of other factors (ie: education of patient's knowledge of procedure, etc). This will help us get an over all view of perceptions/beliefs of patients receiving anesthesia care.

VII.D.23 *Will this information be shared with anyone outside the UI research team members?*
No

VII.D.25 *After the subject agrees to participate (signs consent), are there any screening procedures, tests, or studies that need to be done to determine if the subject is eligible to continue participating?*
No

VII.D.27 *Discuss how much time a potential subject will have to agree to consider participation and whether or not they will be able to discuss the study with family/friends before deciding on participation.*
They will have the amount of time needed to make an informed consent estimated at 20 minutes.

VII.D.28 *How long after the subject agrees to participate do study procedures begin?*
The procedure will begin shortly afterwards (within 15 minutes) as there is time constraint with preparing the patient for the operating room and not delaying arrival time into the operating room.

VII.D.29 *Provide a description of the enrollment and consent process for adult subjects*

- *Describe each study population separately including control population*
- *Include when recruitment and consent materials are used*
- *Use 3rd person active voice "The Principal Investigator will identify subjects. For example, the principal investigator will identify potential subjects, the study coordinator will discuss the study with subjects over the telephone and schedule the first study visit, etc..."*
- *Describe the steps that will be taken by the research team to minimize the possibility of coercion or undue influence during the consent process*

Patients receiving thoracic epidural analgesia; 1) for pain control after major thoracic and abdominal surgeries in the main operating room, 2)for pain control after rib fractures in the in-patient care units, aged between 18 to 75 years will be included in this study. The patients will be divided into 2 groups randomly. One group will receive thoracic epidurals in the traditional way (control group) and the other one with Compuflo assistance. Patients with contraindication to thoracic epidural anesthesia, allergy or hypersensitivity to local anesthetics, Patients unable to provide written informed consent ,Pregnant women and prisoners, Patients with significant valvular heart disease will be excluded from the study.
The surgery schedule for the University of Iowa Hospitals and Clinics (UIHC) Main OR will be reviewed 3-5 days in advance to identify potential study subjects. Charts will be reviewed for inclusion and exclusion criteria. For patients with rib fractures needing epidurals, Consults are received by the Acute Pain Service as part of their work flow. The chart will be reviewed at this time to determine eligibility for the study.
After chart review for eligibility, On the day of procedure, a research team member will approach the patient and talk to them about the possibility of them taking part in a study. The research team member would explain to the patient that they are eligible to take part in a study (related to epidural placement) today. If the patient indicates their consent to hear more and possibly enroll in the study, the research team member will then explain the study, ask the pre-screening questions and obtain informed consent.
They will be told that their decision to participate in the research will not affect the clinical care they receive so as to minimize the possibility of coercion. Time will be allowed for patients to deliberate study participation and discuss with family/friends.
An offer of thoracic epidurals will be provided to all patients unless contraindicated regardless of their decision to participate or not.

Some subjects may be identified from responses to the Iowa Clinical Research & Trials website.

If the patient indicates their consent to hear more about the study & possibly enroll in the study, a representative from the research team will then meet with them to explain the study in a private room/area, go over the informed consent summary, obtain informed consent after the patient has been given time to review consent, ask questions and make an informed decision to participate. Patient will be give a copy of the consent summary & the signed consent.

VII.D.37 *Does the study include any form of deception (e.g., providing participants with false information, misleading information, or withholding information about certain study procedures)?*

Examples:

- *Procedure includes a cover story that provides a plausible but inaccurate account of the purposes of the research.*
- *Participants will be provided with false information regarding the particular behaviors of interest in the research.*
- *Procedures include a confederate pretending to be another participant in the study.*
- *Participants will be told that the research includes completion of a particular task, when in fact, that task will not be administered.*
- *Study is designed to introduce a new procedure (or task) that participants are not initially told about.*
- *If yes, a waiver of informed consent must be requested under question IV.3.*

No

VII.E. Project Description (E)

VII.E.1 *Will subjects be randomized?*
Yes

VII.E.1.a *Will any subjects be blinded to which study arm they have been assigned?*
Yes

VII.E.1.b *Does the protocol permit telling subjects their treatment assignment at the end of the entire study?*
Yes

VII.E.1.c *Describe the circumstances under which subjects will be told what study arm they have been assigned.*
If patients request to know the treatment assignment after completion of the entire study, we will disclose details as needed.

VII.E.2 *Describe randomization scheme/assignment including ratio such as 1:1, 2:1 etc.*
1:1

VII.E.3 *Will any questionnaires, surveys, or written assessments be used to obtain data directly from subjects in this study?*
No

VII.E.5 *Does this project involve creating any audiotapes, videotapes, or photographs?*
No

VII.E.6 *Provide a detailed description in sequential order of the study procedures following the consent process - DO NOT cut and paste from the Consent Document.*

Describe study populations separately if they will be participating in different procedures - include CONTROL population if applicable.

DESCRIBE:

- *What subjects will be asked to do/what happens in the study (in sequential order)*
- *The time period over which procedures will occur*
- *The time commitment for the subject for individual visits/procedures*
- *Long-term followup and how it occurs*

After the consent process, if a patient agrees to participate:
Per usual workflow:
The patient is prepared by the anesthesia clinicians and perioperative nurses for epidural placement.
A timeout for safety will be performed before the procedure starts(per routine).
The epidural procedure will be carried out.

Epidural placement procedures can take anywhere from 10 to 25 minutes not including setup/preparation time.

Per study protocol (These are things which are not part of standard clinical care. They are conducted for patients participating in the study)
A.Patients will be randomized to two groups prior to epidural placement.
The technical description of how epidurals are placed in each group are described in section I.4

B.The following data variables will be collected for the study purpose:

1. Primary outcome variable:
Successful Epidural: Success will be defined as a block to cold (ice)in at least two dermatomes bilaterally within 20-minutes following administration of epidural test dose. Patients will be tested at 10 minute intervals till loss of cold sensation is obtained for a maximum duration of 20 minutes

Failed Epidural: Failure of block to ice after epidural test dose within 20 minutes or failure to identify the epidural space and successfully place a catheter.

Details of the test dose: Patients will receive 3 ml of 1.5% lidocaine with 1:200,000 as the initial dose (T0). They will receive an additional 3 ml of the same test dose after 5 minutes (T5) once intrathecal placement of the catheter is ruled out by testing for lower extremity weakness.They will be tested for loss of cold sensation in thoracic dermatomes at 10 minute intervals (T10 & T20) for 20 minutes.

2.Secondary outcome measures
- Time taken for the procedure (Tuohy needle puncture to removal, opening of supplies to Tuohy needle removal).
- Time taken for loss of cold sensation
- Unintentional dural puncture or other complications (Local anesthetic toxicity or subdural/intrathecal/intravascular injection)
- Assessment of pressure levels and waveform in the Compuflo group
- Hemodynamic changes associated with test dose
- Meniscus test results in 2 groups
- Ease of catheter placement/threading after loss of resistance
- Opioid usage and Pain scores for the first 48 hours will be obtained from the EPIC data

The patient will not have to do anything differently because of the study.
There is no long term follow-up necessary with these patients.

VII.E.7 ***Will you attempt to recontact subjects who are lost to follow-up?***
No - those lost to followup will not be recontacted

VII.E.9 ***Will subjects be provided any compensation for participating in this study?***
No

VIII. Risks

VIII.1 ***What are the risks to subjects including***
- emotional or psychological
- financial
- legal or social
- physical?
Providing a thoracic epidural for major thoracic or abdominal surgery or for patients with rib fractures is a standard procedure performed by the Acute Pain Service.
As we are performing a standard procedure that is always performed, on the study patients, there is no increased risk to the patient.

Complications with neuraxial (Spinals and epidurals) procedures in general:
Unintended dural puncture (For epidurals only) - 1%
Nerve injury:
-Incidence of nerve injury: 0.001% to 0.007% in general population; 0.3% to 1.1% in patients with pre-existing neurological problems.
-Permanent nerve injury: 1 in 5,800 to 1 in 12,200
-Paraplegia or death: 0.7-1.8 in 100,000
Bleeding:
-Spinal hematoma: 1 in 200,00 to 1 in 3,600
-Spinal hematoma needing emergency decompressive laminectomy: 1 in 8,0000
Infection:
-Epidural abscess: 1 in 24,000
-Meningitis: Lower than the incidence of abscess

VIII.2 ***What have you done to minimize the risks?***

- ***If applicable to this study ALSO include:***
  - ***How you (members of your research team at Iowa) will monitor the safety of individual subjects.***
  - ***Include a description of the availability of medical or psychological resources that subjects might require as a consequence of participating in this research and how referral will occur if necessary (e.g. availability of emergency medical care, psychological counseling, etc.)***

We will have a independent safety monitor watch our results. Our results will be monitored and reviewed after 74 patients. If complications appear to exceed the published rates, this will be a stopping point for our safety officer.
Once the epidural is placed, we follow these patients daily till their epidural catheter is in-situ to manage their pain control. In addition, we have a post-block clinic in the Ambulatory Surgery Center to see all patients who have regional anesthesia related complications. Should this occur with a study patient, they can be evaluated promptly there.

All patients having regional anesthesia for this study will be done in a setting with standardized monitors and oxygen. Emergency equipment is available at all times that regional anesthesia is being administered as well as intralipid immediately available for inadvertent intravascular local anesthestic injection.

VIII.3 ***Does this study have a plan to have an individual or committee review combined data from all subjects on a periodic basis (such as summary or aggregate safety and/or efficacy data)?***
Yes

VIII.4 ***Describe the plan to review combined data from all subjects, such as summary or aggregate safety and/or efficacy data. Include the following:***

- ***Describe what data will be summarized and reviewed***
- ***Describe how frequently data will be reviewed.***

The data will be looked at after data for half the patients in the study (74) is collected. We will look at the rate of complications for the patients in the study and make sure that they do not exceed the published risks for thoracic epidurals. Risks include:
1.Unintended dural puncture - 1%
2.Nerve injury (< 0.1%)
3.Paraplegia or death (<0.01%)
4.Bleeding -Spinal hematoma (<0.1%)
5.Infection (<0.1%)
-Epidural abscess
-Meningitis

VIII.5 *Will overall safety monitoring be performed by individual(s)/committee at The University of Iowa. (NOTE: If this study involves more than minimal risk, in most cases these should be individuals who are not members of the study research team.)?*
Yes

VIII.6 *List names:*
David Swanson MD, Emine Bayman PhD or Bradley Hindman MD

VIII.7 *Will overall safety monitoring be performed by individuals or committee not associated with The University of Iowa (such as a study Data Safety Monitoring Board)?*
No

IX. Benefits

IX.1 *What are the direct benefits to the subject (do not include compensation or hypothesized results)?*
There are no direct benefits to the subject from participating in the study.

IX.2 *What are the potential benefits to society in terms of knowledge to be gained as a result of this project?*
Society may potentially benefit from the new knowledge generated by having an epidural technique with a better success rate. Knowing the technique with least failure rate will help to take care of patients in future better. Choosing the epidural technique with the higher success rate will help in better management of pain in these patients.

X. Privacy & Confidentiality

X.1 *What are you doing to protect the privacy interests of the subjects?*
The procedure is done in area where patient privacy is maintained & we will maintain this protocol. We will only be collecting minimal information necessary to conduct this research & limiting access to the research team members.

X.2 *Are you collecting the Social Security Number of any subjects for any purpose?*
No

X.4 *How will information/data be collected and stored for this study (check all that apply):*

- Electronic records (computer files, electronic databases, etc.) - Electronic records (computer files, electronic databases, etc.) will be kept on the password protected Anesthesia department server. The members of the research team will be the only ones with access to the files. All patients will be assigned a study number de-idenified. The data will be stored in a locked database and office on the UIHC Dept of Anesthesia server, password protected. We will also use Redcap electronic records for data collection, which is password and user-assigned protected database.
  - Name - David Griffiths
  - Title - Senior Systems Administrator
  - University Job Classification - Faculty/Staff
- Paper/hard copy records (hard copy surveys, questionnaires, case report forms, pictures, etc.) - Hard copy records will be kept in a locked cabinet within a locked office in Anesthesia Dept. only accessed by research personel. All identifying information will be coded to keep study data confidential. Any patient not enrolled in study will be destroyed after it's entered into the declined log on the Anesthesia sharedrive network folder specifically for this study.

X.5 *Do the confidentiality protections indicated above allow only members of the research team to access the data/specimens?*
No

X.6 *Describe*
The success rate using CompuFlo technology for thoracic epidural cathcter insertion vs traditional insertion approaches is of interest to Milestone Scientific. This de-identified information will be shared with Milestone Scientific who in turn has requested Knoell Medical Devices, LLC. to complete the data analysis.

X.7 *Does your study meet the NIH criteria for a Certificate of Confidentiality or will you be applying for Certificate of Confidentiality?*
No

XI. Data Analysis

XI.1 *Describe the analysis methods you will use, including, if applicable, the variables you will analyze*
A.Primary outcome variable:
Success rate of thoracic epidural placement will be the primary endpoint.
The primary aim of the study is to show the superiority of the 'CompuFlo technique' (CT) over the 'Traditional technique' (TT) in terms of success rate. The epidural will be considered a success if there is loss of cold sensation in at least one dermatome bilaterally. The success is defined as success vs failure, and will be tested between CT and TT groups by chi-square test or Fisher's exact test.

B.Secondary variables:
- Time taken for the procedure (Tuohy needle puncture to removal, opening of supplies to Tuohy needle removal).

- Unintentional dural puncture or other complications (LA toxicity or subdural/intrathecal/intravascular injection)
- Assessment of pressure levels and waveform in the Compuflo group
- Hemodynamic changes associated with test dose
- Meniscus test results in 2 groups
- Ease of catheter placement/threading after loss of resistance
- Measure(s) of postoperative analgesia success such as pain scores and opioid consumption.

XI.2 ***Provide the rationale or power analysis to support the number of subjects proposed to complete this study.***

Based on the previous studies, we expect the success rate with the TT to be 75%. We expect the success rate for the CT group to be 95% to be clinically meaningfully different from TT (95% success rate in CT vs 75% success rate in TT). To achieve 80% power, with a two-sided type I error rate of 0.05 with these success rates (75% vs 95%), we need 49 subjects per group; 98 patients total. We plan to enroll 120 patients having a conservative attrition rate of 20% given the fact that we are studying the use of a device in a training institution. In addition, the study protocol was revised after the inclusion of the first 13 patients. Hence we need to enroll 133 patients to complete the study.

The original Data Use agreement provided provisions for de-identified data to be shared with Milestone Scientific, Ins. for the purpose of a supplemental submission use to the US FDA. Milestone now requests that Knoell Medical Devices, LLC be the entity to do this analysis. A modification to the Data Use Agreement is currently underway through the University of Iowa Division of Sponsored Programs.