

Response to the ethics review:

In accordance with the discussion at the ethics review, the protocol has been revised to include statements defining that the consent will be obtained by an interventional radiologist who will not be performing the procedure. As well an age criteria has been added. Finally, as suggested, in order to blind the patient further, a curtain will be drawn between the eyes of the patient and the operating field where the nerve block or sham procedure will be done. This version (version 3) has now been uploaded to the system. The only difference between this protocol and Version 2 are the modification of these specific elements that were brought up by the ethics committee. Also clarification regarding the principal investigators and collaborators is done.

The modified consent form will also be uploaded to the system (version 2) as requested by the ethics committee.

Thank you very much for your suggestions. I trust these modifications will satisfy fully the requests of the ethics committee.

Sincerely,



Louis-martin Boucher

**Prospective blinded study looking at PO/IV analgesia alone
versus PO/IV analgesia with superior hypogastric nerve block
for uterine artery embolization pain management**

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Date of Original Protocol: Oct 10th, 2014

Protocol Version: Ver3

Revision History:		
Revision	Description	Date
Ver1	Initial version	Oct 10 th , 2014
Ver2	Revision following scientific review Revisions include 1) Explanation of UFE procedure 2) Statistical analysis modifications	Nov 29 th , 2014
Ver3	Revision following ethic committee review Revisions include 1) Clarification on obtaining the consent which will be done by someone who is not performing the procedure itself and that separate consents will be obtained for the UFE and for the research protocol 2) Age will be added to the inclusion criteria 3) The patient's view will be blocked during the procedure so that they do not see whether the nerve block or the sham procedure is performed.	Dec 2 nd , 2014

Confidentiality Statement

This document may be disclosed to appropriate Institutional Review Boards/Independent Ethics Committees or duly authorized representatives of Regulatory authorities, but otherwise should remain confidential.

Protocol Signature Page

Protocol Title Prospective blinded study looking at PO/IV analgesia versus PO/IV analgesia with superior hypogastric nerve block for uterine artery embolization pain management

Protocol No. 1

Protocol Version Ver3

Protocol date Dec 2nd, 2014



Dec 2nd, 2014

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Abbreviations used:

CRF	Case Report Form
UAE	Uterine artery embolization
IRMD	Interventional Radiology Medical Doctor
IV	Intravenous
PO	Oral Administration
REB	Research Ethics Board
SAE	Serious Adverse Event
SHGNB	Superior Hypogastric Nerve Block

PROTOCOL SYNOPSIS

Title	Prospective blinded study looking at PO/IV analgesia alone versus PO/IV analgesia with superior hypogastric nerve block for uterine artery embolization pain management
Protocol No.	1, Ver 3
Principal Investigators & Study Sites	Louis-Martin Boucher, MD -Montreal General Hospital David Valenti, M.D. - Royal Victoria Hospital Tatiana Cabrera, M.D. –Royal Victoria Hospital Carlos Torres, M.D. –Montreal General Hospital Karl Muchantef, M.D. – Montreal Children Hospital Benoit Gallix, M.D. –Royal Victoria Hospital
Study Objectives	<p>1. The primary objective is to assess whether the use of a superior hypogastric nerve block performed during uterine artery embolization procedures helps provide better pain management than oral/IV medications alone by assessing patient directed pain scoring and differences in use of oral/IV analgesics</p> <p>2. As secondary objectives the group with the sham procedure and those with the superior hypogastric nerve block will be compared for rate of adverse events, differences in pain/complication related hospital admission/re-admission rates, differences in pain control as related to the bulk volume of fibroids, differences in pain control as related to fibroid disease versus adenomyosis, successful outcome of embolization procedure, successful relief of patient symptoms from the fibroids at time of follow-up</p>
Study Design & Procedure	<p>This is a prospective double-blinded randomized comparative trial. Experienced interventional radiologists at the MUHC will carry out all intervention.</p> <ul style="list-style-type: none"> • 50 consecutive subjects meeting the eligibility criteria, scheduled for uterine artery embolization for symptomatic uterine fibroids and/or adenomyosis. • Consent will be obtained from all patients by a interventional radiologist who will not be involved in the procedure itself. • All procedures will be performed by a qualified interventional radiology medical doctor (IRMD). • Patients who accept to participate and fit the criteria will be randomized to either receive a superior hypogastric nerve block (SHGNB) during the procedure or simply injection of xylocaine in the skin at the periumbilical subcutaneous tissues (sham procedure). • The hypogastric nerve block or sham procedure will be performed by an independent interventional radiologist while the primary operators (radiologists and support staff) of the uterine artery embolization are removed from the room. Once the block or sham procedure is completed, the primary operators returns to the room to

	<p>complete the uterine artery embolization.</p> <ul style="list-style-type: none"> • The patients view of the procedure will be blocked during this time to ensure they are not aware of whether they have had a nerve block or simply a sham procedure • The patient will be offered IV analgesia using midazolam and fentanyl during the procedure at set regular intervals • Similar analgesics as well as per oral analgesics will be provided as per set orders during the recovery period in the post-procedural recovery room • The patient will be discharged home with standard prescriptions for home analgesics which include routine medication and medication to be used for breakthrough pain. • At home, the patient will be filling out an online or paper survey to monitor use of medication and assessment of pain on a visual analogue pain scale. To preserve anonymity of patients deciding to fill out the online survey, the patient will be assigned a anonymous number to be used to log into the survey system prior to leaving the hospital • Data will be gathered, stored, and analyzed. • Follow-up of the patient will occur as per routine 4-6 months post embolization to assess the clinical success of the procedure. <p>Subject data collection on the day of the procedure will include demographics, relevant medical history, vital signs, use of IV analgesics, use of oral analgesics, use of SHGNB or sham procedure. Subject data collection while at home will include visual analogue pain scale and self-recording of medication intake.</p>
<p>Study Rationale</p>	<p>Uterine fibroids have a significant negative impact on the quality of life of many women who are in their reproductive years. Problems associated with uterine fibroids include excessive blood loss during menstruation (menorrhagia) with often irregular menstrual periods (menometrorrhagia), in some cases leading to marked anemia and need for blood transfusions, excessive pain especially during menstruation (dysmenorrhea), and symptoms of bulk causing compression on the bladder and increased urinary frequency often with waking up at night to urinate (nocturia) or even incontinence, or compression of the rectum causing constipation. As well many women suffer from painful intercourse (dyspareunia), which can have negative impact on self-image and marital status. These symptoms can be very debilitating, and are often career limiting.</p> <p>Until relatively recently, most of these women had to opt for hysterectomy to help control these symptoms. However in the late 1990s, several publications demonstrated the feasibility of uterine artery embolization to control these symptoms. By blocking the blood flow to the fibroids, the fibroids became necrotic and the symptoms resolved. Since then the technique has become widely accepted as a less invasive alternative to surgery with excellent clinical results.</p>

	<p>The biggest complication of the embolization is that of pain, which is almost universal. The embolized fibroids lead to significant discomfort gradually decreasing over a period of 7-10 days, with most of the discomfort being present in the first 24 hours. Because of this, many centers still routinely admit their patients overnight with patient controlled analgesia or with epidural analgesia catheters in place. However, because of constraints caused by admission availability, many centers are exploring better regimens of analgesia that would allow patients to go home on the same day as the procedure. Here, at the MUHC we have an analgesia protocol that allows approximately 90% of our patients to be discharged home on the same day, often with significant but tolerable discomfort. However there is much room for further pain control improvement to increase the rate of discharge, to improve pain control amongst discharged patients, and to reduce the rates of return visits to the emergency department and re-admissions due to uncontrolled pain while at home.</p> <p>The superior hypogastric nerve plexus is a primary plexus relaying pain information from pelvic structures, including the uterus. A block of this neural plexus is a well-established technique used in cases of chronic pelvic pain such as that caused by pelvic-based cancers. In 2004, a group from Ottawa published a report using this type of nerve block to control the pain associated with UAE. They placed a very small-gauged needle via a periumbilical anterior approach down to the nerve plexus anterior to the lumbosacral vertebral body and injected a long acting anesthetic agent called bupivacaine in the plexus. They reported a significant improvement in pain control with all their patients being able to be discharged and only a very small proportion needing to return to the hospital because of uncontrolled pain. They have had no significant complications attributed to the nerve block procedure itself. However their study was not a formal comparative study.</p> <p>Here at the MUHC, we have used this technique in several patients with promising initial results, but the procedure remains semi-invasive and we believe needs validation especially since pain is such a subjective symptom. This lack of formal validation is probably why the technique is slow to be adopted by other groups. We believe this study will allow a final conclusion regarding the use of this technique in the treatment of uterine fibroids embolization.</p> <p>The goal of the study is to compare the pain sensations patients have and need for analgesics post uterine artery embolization for fibroids by generating a double blinded situation in which neither the patient or primary operator of the embolization are aware of whether the block has been performed or not.</p>
<p>Planned Sample Size</p>	<p>Based on published data, the average pain felt by ladies post uterine artery embolization is 7/10 with a standard deviation of approximately 2.5. The published study of SHGNB for UAE demonstrated a decrease in pain from 7 to 2-5 depending on the analgesics regimen used. We</p>

	<p>opted for the conservative drop in pain scale from 7 to 5 with a standard deviation of 2.5. This gives an effect size of 0.8. With type I error (alpha) set at 0.05 and type II error (beta) set at 0.2 (power of 80%), the sample size calculations yields a needed sample size of 42. We expect up to a 20% drop out rate due to loss to follow-up, giving a total sample size needed of 50, leaving 25 patients per group.</p> <p>Since the pain drop can be more significant than the conservative value we have opted to use, we suggest an interim analysis that would be expected to give us statistical significance if the pain scale was improved by 50% from 7-3.5 (4 being the number usually used by the recovery room to decide to release patients). Based on similar calculations, to show this level of improvement (taking in account a similar drop out rate), one would need a total of 20 patients and therefore we plan on doing an interim analysis at 20 patients having completed the study to see if there is any need to continue the study or not.</p>
Inclusion Criteria	<ol style="list-style-type: none"> 1. Women with symptomatic fibroids or adenomyosis that have requested and been approved for uterine artery embolization 2. Age of patients ranging between 35 and 60 years old 3. Ability to comply with the requirements of the study procedures
Exclusion Criteria	<ol style="list-style-type: none"> 1. Patients in whom the vascular anatomy prevents access to the superior hypogastric nerve plexus safely 2. Patients who have known allergy to the anesthetic agent 3. Patients with signs of skin infection at the entry site of the needle used to place the nerve block 4. Patients with signs of infection such as fever 5. Patients with history of inflammatory bowel disease or with signs of colitis 6. Patients with uncorrectable abnormal coagulation status (INR >1.5 and plt < 50000 without use of anticoagulation agents) 7. Patients with preexisting conditions, which, in the opinion of the investigator, interfere with the conduct of the study. 8. Patients who are uncooperative, cannot follow instructions, or who is unlikely to comply with follow-up appointments or fill-out the post-procedural pain questionnaires. 9. Patients with mental state that may preclude completion of the study procedure or be unable to provide informed consent
Schedule of Study Visits	<p>No change from routine schedule presently used:</p> <ol style="list-style-type: none"> 1) MRI pre-UAE 2) Consultation pre-UAE (consent will be obtained at this time) 3) UAE procedure (not usually the same day as the consultation) 4) MRI 4-6 months post-UAE 5) Consultation post-UAE after post-UAE MRI completed
Efficacy Outcome	<ul style="list-style-type: none"> ▪ Primary: <ul style="list-style-type: none"> ○ Reduction in pain as measured by patient self administration of visual analogue scale

	<ul style="list-style-type: none"> ○ Reduction in use of oral analgesics at home and IV/oral analgesics while in hospital ▪ Secondary: Comparison of sham versus SHGNB group to look for <ul style="list-style-type: none"> ○ Differences in adverse events ○ Differences in pain/complication related admissions ○ Differences in pain in relation to total volume of fibroids ○ Differences in pain in relation to fibroids versus adenomyosis ○ Differences in successful outcome of the embolization both by imaging and clinically ○ Use of the online questionnaire vs the paper questionnaire
Safety	<ul style="list-style-type: none"> ▪ Possible adverse events the SHGNB would include: <ul style="list-style-type: none"> ▪ Infection ▪ Bowel injury ▪ Vascular injury/Bleeding ▪ Pain or nerve injury ▪ Allergic reaction to the anesthetic agent ▪ Intravascular injection of the anesthetic agent which can lead to cardiac arrhythmias or seizures ▪ Hospitalization or emergent surgery <p>The rate of significant complications is estimated to be less than 0.5%.</p> <p>In the sham group, the only significant risks would be infection and allergic reaction to the anesthetic agent.</p> <ul style="list-style-type: none"> ▪ Expected possible adverse events of the uterine artery embolization, independent of SHGNB or not <ul style="list-style-type: none"> ▪ Pain ▪ Vascular injury/Bleeding ▪ Embolization material migrating to non-targeted organs ▪ Premature ovarian failure ▪ Uterine infection leading to possible hysterectomy ▪ Pulmonary Embolus ▪ Leaving a uterine sarcoma unresected <p>Other than pain, which is almost universal and premature ovarian failure that can occur in 2-10% of patients, the other risks are in the order of 1-2% or less. Other than pain, it is expected that these complications will be independent of whether a SHGNB is</p>

	<p>performed or not.</p> <p>Subjects with procedure related adverse events will be followed up until the resolution of the event.</p> <p>A medical monitor will analyze all serious adverse events (“SAE”) in order to confirm that they are unrelated to the research protocol.</p>
Statistical Methods	<p>Descriptive statistics will be provided for the efficacy outcome results and will be presented in terms of percentage, frequency, means and 95% confidence interval. Differences between both groups will be compared using Chi-square test for categorical variables and, after verifying a normal distribution to the data, a Student’s t- test for the continuous variables. Regression analysis will be performed to compare time dependent events.</p>

1.0 Background

1.1. Uterine Fibroids

Uterine fibroids are a monoclonal tumor of smooth muscle origin. Their cause is unknown but is known to be hormone responsive, being diagnosed only after menarche and decreasing after menopause [1].

Uterine fibroids are the most common pelvic tumors in women being present in >80% of black women and approaching 70% in white women in their late 40s. Of these, 50% of black women and 35% of white women have clinical symptoms caused by the fibroids [1]. In 2008-2009, the estimated rate of hysterectomies in Canada was 338/100000 women > 20 years old, with an estimated \$192 million dollars in associated hospitalization costs (Canadian Institute for Health Information). Of these, abnormal menstrual bleeding and fibroids remain the most common reason for hysterectomies. The most common clinical symptoms associated with fibroids are increased bleeding during menstruation, increased pelvic pain especially during menstruation or sexual intercourse, and pressure effects on surrounding structures causing increased urinary frequency and constipation. These symptoms can be very debilitating.

Fibroids are almost exclusively benign in nature. However they can be difficult to differentiate from malignant sarcomas. Fortunately such sarcomas are rare, being estimated at 0.2% or less in surgical series [2].

1.2. Uterine artery embolization

In view of the low risk of malignancy and the complications and cost associated with hysterectomies, there has been a push towards less invasive approaches to treat fibroids. In the mid-late 1990s, the first few publications were released presenting intra-arterial embolization as a method to deplete the fibroids of their blood supply and induce their necrosis, to treat symptomatic fibroids [3]. The procedure consists of obtaining intra-arterial access as is performed routinely for angiographic studies. A catheter is advanced into the uterine arteries on both sides and small plastic based particles are injected. The particles are carried by the blood to the fibroids where they act as plugs as the vessels divide and reduce their size, becoming smaller than the particles themselves. By doing this, the arterial blood supply to the fibroids can be blocked. The result is ischemic fibroids that then undergo necrosis.

The procedure used for the UFE is the same as is presently used at the MUHC. It is performed in the angio unit with the help of fluoroscopy. Access is obtained in the right common femoral artery followed by placement of a vascular sheath. Through the sheath, a 4Fr DAV or 5Fr Cobra catheter and guidewire are used to cannulate the uterine arteries. If there is evidence of spasm, a microcatheter is used. Once the catheter is advanced into the horizontal portion of the uterine artery, an angiographic image is obtained to confirm absence of non-uterine vessels distal to the catheter, such as vessels feeding the vagina that could be damaged by the embolization. After confirmation that no non-targeted vessels are seen, PVA 500-700 particles, suspended into 15-20 ml of a mixture of 50:50 contrast:saline, are injected slowly into the uterine artery until there is loss of visualization of the fibroid blushes and stagnation of contrast in the uterine artery so that the contrast remains present in the artery for a total of at least 5 heart beats. After the left

artery has been treated, the right artery is treated in the same fashion. After the treatment, the catheters and sheaths are removed, pressure is applied to the groin for hemostasis, and the patient is transferred to the recovery room.

The UFE procedure has been found to be safe and effective with fewer complications than total hysterectomy. Approximately 80-90% of women get clinical improvement after uterine artery embolization and 97% would recommend the procedure to others [4]. The most common complication which is almost universal, is that of pain post embolization.

1.3. Pain from Uterine artery embolization

When UAE was first started, the need for pain control was evident. Although it was initially done with general anesthesia in the USA, it was quickly found that this was not necessary. However almost everyone admitted the patient overnight with morphine based patient controlled analgesia (PCA). The use of PCA pumps allowed careful assessment of the pain course after UAE. The information gathered shows a maximal pain threshold reached at approximately 2 hours post-procedure, which lasts 3-4 hours and then a gradual decrease to a lower plateau over another 4-6 hours. This period of decrease to a lower pain plateau is the time during which attempts at discharging the patients from the hospital with oral pain medication is attempted [5]. Most women declare no longer having embolization related pain after 7-10 days.

Because of limited availability to hospital admission after radiological procedures at the MUHC, and the need to offer this less invasive treatment of uterine fibroids to women, the interventional radiologists at the MUHC have offered the procedure with an aggressive IV/Oral sedation protocol while in recovery and discharge orders 4-5 hours after the end of the procedure. The patients are sent home with oral pain medication. However despite this aggressive protocol, approximately 5-10% of patients need admission, not without difficulties at times due to the chronic shortage of beds. This is primarily because this time point of attempted home discharge from the recovery room is still in the phase where the lower more tolerable pain plateau, usually reached only approximately 8 hours after the procedure, has not been reached yet. Even in those that are successfully sent home, they report significant discomfort upon discharge from the hospital and there are some that return to the emergency department for pain management.

In addition there is very little published data regarding pain management once the patients have been discharged home. In an attempt to evaluate this, we have established an online survey that patients can voluntarily fill out to allow us to evaluate this in the future and to flag patients having significant pain, so as to offer a better service to these patients. The patients sign in using an anonymous number assigned to them on the day of the UAE. We would be using this survey in this study and as secondary goal, we will be assessing ease of use of this survey by the patients. Alternatively, the patients can fill a paper based survey if they prefer.

1.4. Superior Hypogastric Nerve Block

Because of the difficulties dealing with pain post UAE, recently a group in Ottawa has applied a technique used previously to treat chronic pelvic pain from pelvic tumors to control the acute pelvic pain associated with UAE[6]. This consists in doing a nerve

block at the superior hypogastric nerve plexus using a long acting anesthetic agent called bupivacaine. The medication has a duration of action of 4-8 hours which can cover the first high pain plateau until the lower pain plateau is reached. Using the hypogastric nerve block and an aggressive PO analgesia protocol, they have been able to obtain a 100% discharge from the hospital with patients feeling only mild or no pain at time of discharge. There was a 5% readmission rate due to pain. Their results suggest a significant improvement in pain control compared to same-day discharge protocols without a superior hypogastric nerve block.

The hypogastric nerve block consists of advancing a tiny 21 or 22-gauge needle through the abdomen up to the anterior surface of the vertebral body located below the aortic bifurcation. This is the location of the superior hypogastric nerve plexus. Once there, the anesthetic agent is administered. The potential most serious risks of the procedure would include transgression of bowel loops, leading to theoretical transport of bacteria out of the bowel into the abdomen and associated infection, and intravascular injection of the anesthetic agent, which can lead to cardiac arrhythmias and seizures. In order to limit complications from intravascular injection of contrast, we have opted to use ropivacaine as the anesthetic agent, an agent with better safety profile if intravascular injection occurs and similar duration of action[7]. As well, the use of epinephrine in the anesthetic agent can help identify an intravascular injection by monitoring for an increase in heart rate. Finally, prior to injecting the anesthetic agent, we inject a contrast agent that allows us to identify an intravascular injection under fluoroscopy (which is used for the UAE procedure). The group from Ottawa has had no complications, beyond those that can be explained by the UAE procedure itself, in their published series of 139 patients[6] as well as in the more than 400 patients they have treated so far (personal communication). We have also performed approximately 30 of these procedures, without complications.

Because of the success of the group in Ottawa in performing the SHGNB, we have just recently started to offer this procedure as well. Initial results are also very encouraging with recovery nurses informing us that in general the patients seem to be doing much better with the nerve block in place. However the data remains anecdotal. There have been no studies to date comparing simple oral/IV sedation to SHGNB + oral/IV sedation. For this reason, probably, the procedure has been very slow to be adopted by people who perform UAEs. We believe that, to put this issue to rest, there is a necessity for such a comparative trial and, especially important in the context of a subjective outcome such as pain, it is our belief that a randomized double-blinded control trial is needed to obtain conclusive data. This was the reason this study was put together.

2. Research Question:

Is there a difference in subjective pain score patients experience and in the need for analgesics post uterine artery embolization for fibroids if the patients undergo a superior hypogastric nerve block during the embolization procedure.

3. Objectives:

The primary objective is to assess:

- Reduction in subjective pain as measured by patient self administration of visual analogue scale and reduction in use of oral analgesics at home and IV/oral analgesics while in hospital

The secondary objectives are:

- Differences in adverse events between groups with and without SHGNB
- Differences in pain/complication related admissions between groups with and without SHGNB
- Differences in pain in relation to total volume of fibroids between groups with and without SHGNB
- Differences in pain in relation to fibroids vs. adenomyosis between groups with and without SHGNB
- Differences in successful outcome of the embolization both by imaging and clinically between groups with and without SHGNB
- Differences in admission rates
- Differences in rates of return visits to ER for pain issues
- Patient use and appreciation of the online pain survey

4. Implications:

This comparison trial will provide important new information regarding the role SHGNB could play in pain control in women post UAE. The expected benefits would include increasing the availability of UAE in centers with the radiology resources to offer the procedure but without the ability to admit patients overnight and to some patients for whom pain has been a strong deterrent to proceed with UAE and who want to avoid hysterectomy. In addition, another benefit, if proven to allow increased same day discharge, would be to decrease the admission rate post UAE which could have benefits both for the patient as well as for the hospital, in terms of admission bed management, nursing time and medication usage, and at a financial level.

If the procedure is found not to have benefit, this study will give basis to avoid placing patients at risks of complications from an unnecessary added procedure.

5. Data analysis and sample size Calculation

▪ Data gathering and analysis

Nurses in the recovery room will be provided a specific medication escalation regimen to follow based on a patient-centered pain requirement protocol. At the time of discharge, the patient will be seen by the IRMD who will gather the data regarding the dose and frequency of use of analgesia while in the recovery room. He will review the visual analogue pain scale chart with the patient and get her to rank the pain between a scale of 0 to 10 for the pain felt immediately after the procedure, 2 hours after the procedure has ended, and immediately prior to discharge. The recovery nurses will also have a routine pain scale evaluation prior to giving medication and these will be reviewed. The patient will also be given a folder with a series of sheets of visual pain scales to fill out 3 times a day, at specific times while at home, for up to 10 days. They will be provided with a stamped envelope to return to us once they are all filled out. Alternatively, the patient will be offered an anonymous login ID that will allow them to fill out the forms by internet (using a Canadian based survey web site).

The data will be gathered. Confirmation of the data distribution will be done. A normal distribution is expected, but statistical analyses will be modified

accordingly. We expect that the data analysis will consist of regression analysis of the temporal pain level distribution between the group with and without the SHGNB. Continuous variable data, with normal distributions, subgroup analysis of the secondary objectives will be compared using a Student's t- test.

▪ **Sample size calculation**

Sample size calculations are based on published data showing the average pain felt by ladies post uterine artery embolization being of 7/10 with a standard deviation of approximately 2.5. The published study of SHGNB for UAE demonstrated a decrease in pain from 7 to 5-2 depending on the analgesics regimen used [6]. We opted for the conservative drop in pain scale from 7 to 5 with a standard deviation of 2.5. This gives an effect size of 0.8. With type I error (alpha) set at 0.05 and type II error (beta) set at 0.2 (power of 80%), the sample size calculations yields a needed sample size of 42. We expect up to a 20% drop out rate due to loss to follow-up, giving a total sample size needed of 50, leaving 25 patients per group. [8]

If the analysis of the data after recruiting 50 patients is highly suggestive of an effect but without statistical significance, and if the calculations suggest we could get statistical significance by doubling the number of participants, and there have been no significant adverse events from the nerve block, we would increase the number of patients to 100. If adverse events have occurred, the number would not be increased unless approval by the ethics committee.

▪ **Interim analysis**

The previous sample size has been calculated with a conservative number, but the decrease in pain can be as large as from 7 down to 2 based on previous studies. Therefore the above estimation may necessitate more patients than are needed to prove clinical worthiness of the procedure. Clinically, our group feels that we would proceed with the block if we could get at least a 50% decrease in pain from 7 down to 3.5 (a scale of 4 being the common number used for discharge of patients from the recovery room). If a similar sample size calculations is performed for such a drop, a total sample size of 16 would be needed. With a similar drop out rate it is our feeling that an interim analysis should be performed at a patient study completion number of 20, so as to avoid recruiting an excessive number of patients to prove the value of the procedure. Therefore we would perform an interim analysis at 20 patients having completed the study. If the data is statistically significant the study would be terminated early.

6. Study Population

The target population who will be included to participate in this study is all women referred to us for a UAE procedure.

6.1. Inclusion criteria:

1. Women with symptomatic fibroids or adenomyosis that have requested and been approved for uterine artery embolization
2. Women age 35-60 y.o.
3. Ability to comply with the requirements of the study procedures

6.2. Exclusion criteria:

1. Patients in whom the vascular anatomy prevents access to the superior hypogastric nerve plexus safely
2. Patients who have known allergy to the anesthetic agent
3. Patients with signs of skin infection at the entry site of the needle used to place the nerve block
4. Patients with signs of infection such as fever
5. Patients with history of inflammatory bowel disease or with signs of colitis
6. Patients with uncorrectable abnormal coagulation status (INR >1.5 and plt < 50000 without use of anticoagulation agents)
7. Patients with preexisting conditions, which, in the opinion of the investigator, interfere with the conduct of the study.
8. Patients who are uncooperative, cannot follow instructions, or who are unlikely to comply with follow-up appointments or fill-out the post-procedural pain questionnaires.
9. Patients with a mental state that may preclude completion of the study procedure or is unable to provide informed consent

6.3. Randomization:

A block randomization will be used to assign patients to either the SHGNB or to the sham procedure group. Randomization will be performed using a randomization program and the results placed in independent envelopes. These envelopes will be opened based on order of inclusion into the study and will determine the group in which patients will be placed.

7.1. Study Design and procedures

This is a double-blinded prospective randomized clinical study. All procedures will be performed by experienced interventional radiologists in the two MUHC study centers: Royal Victoria Hospital and Montreal General Hospital. Other Canadian hospital centers have shown interest in this protocol and may be added to the study at later dates.

Upon referral to the angiography department for a UAE, the radiologist will assess the patient to determine if she is eligible for recruitment into the study based on the inclusion and exclusion criteria (see Appendix I). This will be performed at the time of a consultation, which occurs up to three months before the actual procedure. If the patient is eligible, she will be explained the study and provided with an information sheet. She will be allowed to decide immediately whether she wants to participate or will be allowed to think about it and left to decide on the day of the procedure. An informed consent will be signed. The visual analogue scale will be explained as well as the commitment to complete the data sheets and return them, or to use the web service.

On the day of the procedure, a randomization envelope will be opened and the person will be assigned to either the sham procedure group or to the SHGNB group.

For both groups the UAE procedure itself will be identical. During the UAE procedure the patient will be offered IV sedation at the start to the amount of 1 mg of midazolam and 50 ug of fentanyl. Further additional doses will be upon request from the patient only. The patient will be informed to ask for more if she needs it. Prior to giving another dose, the patient will be asked to rank their discomfort on a scale of 0-10.

The UAE procedure consists of embolization of both uterine arteries. The SHGNB is usually performed in between embolization of both sides. Therefore for the SHGNB group, the block will be performed after the left uterine artery has been embolized. Following the block, the right uterine artery will be embolized. Similarly the sham procedure will also be performed at the time between both embolization.

In order to preserve the blinding, the block will be performed by a qualified IRMD, not involved with the UAE. Therefore, after the left uterine artery has been embolized, the UAE operator and accompanying technologists will leave the room. The patients vision will be blocked via a sheet placed in between their eyes and the operating field so that they cannot see what procedure will be done. The second operator will come into the room and perform the sham procedure or the SHGNB based on patient assignment to either group and will then leave the room. The primary operator will then return to complete the UAE procedure.

The sham procedure will consist of depositing a small amount of contrast and anesthetic agent into the subcutaneous tissues of the infraumbilical region. As this procedure will be much faster, the block IRMD will be asked to take some extra time in the process to extend the time to a similar amount of time that is needed for the SHGNB.

In the case of the SHGNB, the infraumbilical region will be penetrated by the same size needle as the sham procedure but advanced deeper, past the subcutaneous tissues into the abdomen up to the spine. Once the target is reached, contrast will be injected to ensure that the tip is in the appropriate location and the anesthetic agent will be injected (0.75% ropivacaine).

For the sake of blinding, the patient will be told that the SHGNB and sham procedure can cause similar symptoms depending on the patient. Some patients feel the discomfort at the skin and others deeper. It is our experience that this is the case, with some patients undergoing SHGNB feeling only the skin puncture. In any case, it is also our experience that the pain felt by either a sham procedure or a SHGNB is very short lived and extremely well tolerated by the patients. By attributing similar symptoms to the sham procedure and telling the patient that some patients have no significant discomfort with the SHGNB other than the crossing of the skin we hope to blind the patient so that she does not know whether only the skin was frozen or whether they have had a SHGNB.

Subject data collection at the time of enrollment will include demographics, relevant medical history and vital signs. Subjects will be followed-up as outlined in Table 1 to assess adverse events related to the procedures and clinical success of the procedure. Individual data collection will be considered complete at the time of the follow-up consultation 4-6 months after the UAE procedure.

7.2. Consent

In this study we would be obtaining written informed consent from all patients. This will be obtained at the time of the first consultation or on the day of the procedure if the patient has had time to read the information package and agrees to it. The consent will be signed outside of the angiography suite and the consent will be obtained by an interventional radiologist at the time of the consultation who will not be involved in the procedure itself. The consent for the embolization will be separate than that for the hypogastric nerve block research project itself.

Table 1: Schedule of Study Procedures

Parameter	Consult up to 3m prior to procedure	Day of the procedure	Time between procedure and follow-up consult	Follow-up consult 4-6 m after procedure
Information package	X			
Informed consent signed	X	or X		
History& exam	X	X		X
Randomization		X		
UAE/block		X		
Recovery with data gathering of time in hospital		X		
Visual pain scale sheets give to patient		X		
Results from visual pain scale sheets gathered from patient			X	or X

7.3. Visit on day of Consult

The following should be done at the initial visit:

- Obtain consent for the uterine fibroid embolization procedure
- Review protocol specific inclusion and exclusion criteria.
- Assess whether patient is able to provide consent or not. If the patient is appropriate for the study, informed consent is obtained. This consent will be obtained by an interventional radiologist who will not be involved in the procedure itself.
- Obtain relevant medical history and current demographic data.

Presence of inclusion criteria and absence of exclusion criteria will be verified on the designated source documents and eCRF.

7.4 Day of the UAE procedure

If consent had not been obtained at the day of the consult because the patient wanted to think about it some more, the patient could be asked at this time whether they want to participate in the study or not. If this is the case, all discussion will occur outside of the angiography room and the patient given information sheet and will be given time to decide whether they would like to participate or not.

If they have decided to participate, a pre-randomized envelope will be opened and will decide whether the patient gets the hypogastric block or the sham procedure. UAE will proceed as per usual. The patient will be recovered for at least 4 hours in the recovery room. Data regarding pain management while in the recovery room will be gathered on the provided information sheets (see appendix). Before discharge, the patient will be seen by one of the interventional radiologists to complete a visual analog pain scale and collect the information that has been gathered. The patient will be provided an anonymization number and reminded to fill out the pain forms at home via hard copy that

she can bring back to us at the time of the follow-up or mail to us (see appendix), or that she can fill out anonymously by internet.

Procedural information will be collected and stored in a secure area for future analysis.

7.5. First 10 days following the procedure

The patient has some pain scoring sheets to fill (3/d for the first three days and the 1/d until day 10 post procedure) which record the amount of pain and the amounts of pain medications used. She can fill them on hard copies provided to her and bring them back at the time of the consult or mail them to us in a prestamped envelope. She can also use a internet anonymous filing system to fill out the forms.

7.6. Follow-up Consult

The patient will be seen in follow-up consult 4-6 months after the procedure as per routine protocol. At that time, the patient is evaluated for successful treatment and for possible delayed complications of the UAE. Also a final questionnaire will be filled out regarding any issues that could have arisen from the SHGNB.

7.7 Protocol Revisions and/or Deviations

With the exception of emergency situations, no changes or deviations in the conduct of this protocol will be permitted.

The Research Ethics Board (REB) that granted original approval for the study must be notified of all changes in the protocol, and must provide documented approval of any change or deviations that may increase risk to the subject, and/or that may adversely affect the rights of the subject or validity of the investigation.

In the event of an emergency, the investigator will institute any medical procedures deemed appropriate. However, all such procedures must be promptly recorded and reported to the REB.

7.8. Data Collection:

Patient data will be reviewed by the research investigator on a routine basis to ensure any adverse events and information gathered were correctly recorded. The following datasheets will be used through-out the study:

1. **Screening Form (appendix 1)** will be completed by the enrolling radiologist and will include demographic data and inclusion and exclusion criteria.
2. **Data sheet at time of UAE (appendix 2)** will be completed by the treating interventional radiologist.
3. **Data sheet at time of discharge from recovery room (appendix 3)** will be completed by the treating interventional radiologist.
4. **Data sheets during the following 10 days post procedure (appendix 4)** will be completed by the patient

5. **Data sheet at time of follow-up consult (appendix 5)** will be completed by the interventional radiologist and the patient
6. **Data sheet regarding symptoms and changes in quality of life caused by the fibroids UFS-QoL questionnaire (appendix 6)** will be completed by the patient at the time of the first and last consultation.

No unique patient identifying information will appear on the screening form that will be coded only by a study identification number. A key linking the patient name and study identification number will be maintained in a separate database. All datasheets will be kept in a locked, dedicated research office. All computer records will be maintained in a password-protected, limited access folder. Paper records will be maintained in a locked, dedicated research office. All patients' charts will be kept in secure storage for 25 years, as required by legislation. All privacy regulations will be respected. Only the research coordinator, principal investigator, and the safety committee will have access to the patient data.

Data integrity will be maintained throughout the study. Logic rules within the database will be used to maximize integrity, and random data validation checks will be performed routinely. The research investigator will review studies and patients' data on a monthly basis to ensure that patient follow-up is proceeding as expected. All cases where the research investigator finds a discrepancy in imaging interpretation or outcome assessment will be reviewed by the Adjudication Committee, consisting of the principal investigators. An independent radiologist from the MUHC will be asked to determine the outcome of a dispute amongst the Adjudication Committee.

8. Data Analysis:

Data will be collected and tabulated using the commercially available JMP10/SAS statistical analysis software (SAS Institute Inc., Cary, NC, USA). Descriptive statistics will be provided for the efficacy outcome results and will be presented in terms of percentage, frequency, means and 95% confidence interval of the means. Differences between both groups will be compared using the Chi-square test for categorical variables and Student's t- test for the continuous variables. ANOVA test and multivariate logistic-regression analysis will be used to compare interplay of more than two variables. Two-tailed p-values of less than 0.05 will be set for statistical significance.

9. Ethical considerations:

Research Ethics approval from the MUHC Research Ethics Board office will be obtained prior to the commencement of the study or related research procedures. All patients will be informed about the data that will be gathered for the study. All patients will have the ability to refuse participating in the study as soon as they are able to evaluate it and give their approval or not. Patients will always be given options to ask questions at any time and questions will be answered in a non-intimidating way so as to try to avoid influencing the patient's decision. At any time, the patient can decide to remove himself from the study. If this is the case, he will receive the standard of care.

No unique patient identifying data will appear on the sheets that will be coded only by study identification number. A key linking the patient name and study identification number will be maintained in a separate database. All datasheets will be kept in a locked, dedicated research office. All computer records will be maintained in a

password-protected, limited access folder. Paper records will be maintained in a locked, dedicated research office. All privacy regulations will be respected. All patients' charts will be kept in secure storage for 10 years. Only the research coordinator, principal investigators, and the safety committee will have access to the patient data. The data will be reviewed by the investigators on a regular basis to ensure that patient follow-up is proceeding as expected and to verify imaging interpretation.

10. Personnel:

1. Research coordinator
2. Safety committee (principal investigator/collaborators, radiologist not involved in study, research coordinator).
3. Adjudication committee (principal investigator and collaborators).

11. Funding:

This study is currently a self-funded prospective randomized trial. There is no formal or in-kind industry support. Patients will not be remunerated for their participation in the study.

12. References:

1. BaIRMD, D.D., et al., *High cumulative incidence of uterine leiomyoma in black and white women: ultrasound evidence*. Am J Obstet Gynecol, 2003. **188**(1): p. 100-7.
2. Parker, W.H., Y.S. Fu, and J.S. Berek, *Uterine sarcoma in patients operated on for presumed leiomyoma and rapidly growing leiomyoma*. Obstet Gynecol, 1994. **83**(3): p. 414-8.
3. Ravina, J.H., et al., *Arterial embolisation to treat uterine myomata*. Lancet, 1995. **346**(8976): p. 671-2.
4. Walker, W.J. and J.P. Pelage, *Uterine artery embolisation for symptomatic fibroids: clinical results in 400 women with imaging follow up*. BJOG, 2002. **109**(11): p. 1262-72.
5. Worthington-Kirsch, R.L. and N.E. Koller, *Time course of pain after uterine artery embolization for fibroid disease*. Medscape Womens Health, 2002. **7**(2): p. 4.
6. Rasuli, P., et al., *Superior hypogastric nerve block for pain control in outpatient uterine artery embolization*. J Vasc Interv Radiol, 2004. **15**(12): p. 1423-9.
7. Akerman, B., I.B. Hellberg, and C. Trossvik, *Primary evaluation of the local anaesthetic properties of the amino amide agent ropivacaine (LEA 103)*. Acta Anaesthesiol Scand, 1988. **32**(7): p. 571-8.
8. Faul, F., et al., *G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences*. Behav Res Methods, 2007. **39**(2): p. 175-91.

Appendix I

Screening information and selection of cases

Last name: ----- **First name:** -----

Date: -----

Date of Birth: ----- (YY/ MM / DD)

Email address: _____@_____.

RVH/MGH # -----

Assigned ID code: _____ - _____ - _____ (MGH/RVH – Initials – # on envelope)

(Fill ID code out later at time of SHGNB)

INCLUSION CRITERIA	YES	No
Referral for UAE		Exclude
Ability to comply with the requirements of the study procedures.		Exclude
Subject expected to be able to give consent at time of UAE?		Exclude
EXCLUSION CRITERIA		
Patient with abnormal anatomy on MRI in which the aortic/IVC bifurcations are not normally seated and cannot be used to assess the position of the SHGN plexus?	Exclude	
Allergy to local anesthetic agent?	Exclude	
Skin abnormality in the periumbilical region that preclude placement of a needle through this area?	Exclude	
Untreated infection at time of UAE?	Exclude	
History of IBD or Colitis?	Exclude	
Abnormal anticoagulation status?	Exclude	
Pre-existing conditions, which, in the opinion of the investigator, interfere with the conduct of the study?	Exclude	
Uncooperative patient or cannot follow instructions, or who is unlikely to return to get the filter removal due to poor compliance to follow-up medical appointments?	Exclude	
Mental state that can preclude completion of the study?	Exclude	

Pre UAE MRI review:

of fibroids (1/2/3/>3): _____

Size of three largest fibroid – (save image on PACS with fibroids labeled)

1) _____ x _____ x _____ (cm) % necrosis: _____

2) _____ x _____ x _____ (cm) % necrosis: _____

3) _____ x _____ x _____ (cm) % necrosis: _____

% necrosis overall: _____

Adenomyosis: No Yes: Focal Diffuse

Ovarian anastamosis: No

Ovarian anastamosis: No
 Left
 Right

Primary symptom from fibroids:

- Menorrhagia
- Bloating
- Increased urinary frequency
- Constipation
- Dyspaneuria
- Other: _____

Attach Patient's UFS-QOL questionnaire

Appendix II - At time of UAE

Identification code: _____

Date of UAE: _____ (YY/ MM / DD)

RVH/MGH # _____ Age: _____

Do not open envelope until ready to do block (i.e. when switch doctors)

Consent signed: Yes No (do not proceed)

UAE PROCEDURAL DETAILS (to be filled by UAE IR without knowledge of Randomization group):

Pain scale at start of procedure (0-10): _____ (time: __:__)

Embolization material and size used: _____

Arteries embolized:

<input type="checkbox"/>	Rt UA	# vial of PVA: _____
<input type="checkbox"/>	Lt UA	# vial of PVA: _____
<input type="checkbox"/>	Rt OA	# vial of PVA: _____
<input type="checkbox"/>	Lt OA	# vial of PVA: _____

Other: _____ # vial of PVA: _____

Total fluoroscopy time of entire procedure: _____

Ovarian artery anastamosis seen?

No
 Left
 Right

Complications during UAE:

Pain (scale 1-10: _____)
 Arterial spasm - artery: _____
 Extravasation - artery: _____
 Groin hematoma

Other: _____

How many sites of injections: 1 or 2 or >2

Immediate complications from SHGNB/SHAM procedure:

Pain - where: _____

Bleeding

Rigors/Fever

Other: _____

IR UAE: _____ IR SHGNB: _____

Technologist: _____

Appendix III - At discharge from recovery room

Identification code: _____

Date of UAE: _____ (YY/ MM / DD)

RVH/MGH # _____ Age: _____

Pain scale at time of arrival to recovery (0-10): _____ (time: __:__)

IV Medications used during recovery (Dose/ time/pain scale at time of giving it):

Fentanyl (Dose/Time): _____ ug _____:_____ /10
 _____ ug _____:_____ /10
 _____ ug _____:_____ /10
 _____ ug _____:_____ /10
 _____ ug _____:_____ /10

Midazolam (Dose/Time): _____ mg _____:_____ /10
 _____ mg _____:_____ /10
 _____ mg _____:_____ /10
 _____ mg _____:_____ /10
 _____ mg _____:_____ /10

Other (Name/Dose/Time): _____ :_____ /10
 _____ :_____ /10
 _____ :_____ /10

Oral Medications used during recovery (Dose/time/pain scale at time of giving it):

Empracet: _____ / _____ : _____ / _____ /10
 Tramacet: _____ / _____ : _____ / _____ /10
 Oxycodone: _____ / _____ : _____ / _____ /10
 Hydromorphone: _____ / _____ : _____ / _____ /10
 Naprosyn: _____ / _____ : _____ / _____ /10
 Other: : _____ / _____ : _____ / _____ /10
 _____ / _____ : _____ / _____ /10

Pain scale at departure from recovery (0-10): _____ (time: __:__)

Admission to hospital

No Yes - Why: _____

Complications while in recovery: _____

Patient D/C with antibiotics No
 Yes (Name/Dosage/Frequency x # Days)
_____ / _____ / _____ x _____ d

Patient D/C meds: (Name/Dosage/Frequency x # Days)

- Empracet / _____ / _____ x _____ d
- Tramacet / _____ / _____ x _____ d
- Oxycodone / _____ / _____ x _____ d
- Hydromorphone / _____ / _____ x _____ d
- Naprosyn / _____ / _____ x _____ d

Other: _____ / _____ / _____ x _____ d
_____ / _____ / _____ x _____ d
_____ / _____ / _____ x _____ d

Inform patient how to fill out pain scales at home and how to do it by internet. Give out the sheets but encourage using internet if possible and patient at ease with this.

If willing to use internet:

Get patient email address: _____@_____.

Patient anonymous login name: _____

(first letter of hospital/tree numbers in assigned ID code (Ex if first patient enrolled and at the RVH – anonymous ID # is R001))

Give out their login name for the anonymous internet access and write down on hard copy pain scale sheets that go with patient. Give out hard copy sheets even if patient wants to use internet.

Send email immediately to patient to link to internet forms.

Appendix IV - Sheets to be filled out by patient

We encourage you to fill out these sheets via the internet if possible using the following anonymous login name and password to sign in. Otherwise you can use these hard copies and mail them back to us in the prestamped envelope or bring them back to your follow-up visit in 4-6 months.

You will receive an email giving you a link to the internet forms

Your anonymous login name for the internet is: _____

Your Password is: _____

Appendix V - At follow-up consult

Post UAE MRI review:

of fibroids (1/2/3/>3): _____

Size of three largest fibroid labeled on pre UAE consult

1) _____ x _____ x _____ (cm) % necrosis: _____

2) _____ x _____ x _____ (cm) % necrosis: _____

3) _____ x _____ x _____ (cm) % necrosis: _____

% necrosis overall: _____

Adenomyosis No Yes: Focal Diffuse

% necrosis of adenomyosis: _____

Ovarian anastamosis: No
 Left
 Right

Complications since the UAE:

Persistent Pain - Where: _____

Arrested periods - Since when: _____

Vaginal bleeding outside of periods

Symptoms of peri-menopause (hot flushes, nights sweats, etc)

Since when: _____

Endometritis - treated when: _____

Other infection – where: _____ treated when: _____

Need for surgery - When: _____

Why: _____

Continued symptoms as they were before the UAE (no clinical improvement)

Other: _____

Clinical outcome of UAE:

- Complete resolution of symptoms
- >80% improvement in symptoms
- 50-80% improvement in symptoms
- 20-50% improvement in symptoms
- <20% improvement in symptoms

Is patient happy with the outcome (scale 0-10): _____

Attach Patient's UFS-QOL questionnaire

Appendix VI - UFS-QoL questionnaire

See: Spies et al. 2002. The UFS-QOL, a new disease-specific symptom and health-related quality of life questionnaire for leiomyomata. *Obstet Gynecol.* 99(2):290-300.