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# Uterine fibroid characteristics and intraoperative analgesic requirements during high intensity focused ultrasound therapy at a central hospital

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# Uterine fibroid characteristics and intraoperative analgesic requirements during high intensity focused ultrasound therapy at a central hospital

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg in partial fulfilment of the requirements for the degree of Master of Medicine in the branch of Anaesthesiology

Johannesburg 2019.

**Declaration**

I, Anjeanette Ferreira, declare that this Research Project is my own, unaided work. It has been submitted for the Degree of Master of Medicine in the branch of Anaesthesiology at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other university.

_____

1st March 2019 in Johannesburg

## Dedication

This thesis is dedicated in memory of my beloved father, Matie Ferreira and to my mother, Marieta Ferreira who has been my unwavering support.

## Abstract

### Background

Uterine fibroids affect 25% ─ 44 % of women of reproductive age. High intensity focused ultrasound (HIFU) is a non-invasive treatment for fibroids, that is becoming increasingly popular as it has many advantages over surgical procedures. The clinical impression at Chris Hani Baragwanath Academic Hospital (CHBAH) is that HIFU therapy for fibroids is very painful.

### Methods

A retrospective, contextual and descriptive study was done reviewing all HIFU records (n=236) at CHBAH from 13 October 2015 to 30 September 2017.

### Results

Of the anaesthetic charts, 223 (94.5%) were available for analysis. Having multiple fibroids increased (p=0.002) the likelihood of requiring higher dosages of short-acting opioids. An increase in treatment time had a high likelihood of resulting in an increase in both short- (p=0.004) and long-acting (p=0.001) opioid requirements and an increase in energy used had a high likelihood of increasing long-acting opioid (p=0.002) requirements. Body mass index (BMI) influenced intraoperative analgesic requirements. Patients who had a normal BMI were likely to require less intraoperative analgesic drugs than those who were overweight and obese.

### Conclusions

Most of the patients presenting at CHBAH for HIFU therapy have multiple fibroids and judging by the of intraoperative analgesia administered, HIFU treatment appears to be very painful, which is not in keeping with most other studies.

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## List of abbreviations

| | |
|---|---|
| AF | Anjeanette Ferreira |
| AMPA | α-amino-3-hydrox y-5-methyl-4-isoxazolepropionic acid |
| BMI | Body mass index |
| COX2 | Cyclo-oxygenase-2 |
| CHBAH | Chris Hani Baragwanath Academic Hospital |
| FDA | Food and Drug Administration |
| FIGO | International Federation of Gynaecology and Obstetrics |
| HCC | Hepatocellular carcinoma |
| HIFU | High intensity focused ultrasound |
| IASP- | International Association for Study of Pain |
| ICMJE | International Committee of Medical Journal Editors |
| ICTRP | International Clinical Trials Registry Platform |
| IV | Intravenous |
| MeSH | Medical Subject Headings |
| MRI | Magnetic resonance imaging |
| NSAID’s | Non-steroidal anti-inflammatories |
| OPD | Outpatient department |
| RCC | Renal cell carcinoma |
| SAJAA | Southern African Journal of Anaesthesia and Analgesia |
| SASA | South African Society of Anaesthesiologists |
| TRP | Transient receptor potential |
| UAE | Uterine artery embolization |
| UFS-QOL | Uterine Fibroid Symptoms and Quality of Life Questionnaire |
| USA | United States of America |
| USG | Ultrasound guided |
| VAS | Visual analogue pain score |

## Section 1: Literature review

### 1. Introduction

In the literature review the knowledge about high intensity focused ultrasound (HIFU) therapy for uterine fibroids will be discussed. It will give background about uterine fibroids, the incidence and prevalence thereof and the different types of uterine fibroids. HIFU therapy is further contextualised into the history of this therapy, the physics behind it, how it is monitored and the uses and limitations of it. A discussion about the literature available on the demographics of patients undergoing HIFU therapy for uterine fibroids, as well as uterine fibroid size and volume treated will then be explored. The literature review will then be concluded with the literature available on pain experienced intraoperatively during HIFU therapy and the management thereof.

### 1.2. Definitions

#### 1.2.1 Uterine fibroids

Uterine fibroids are benign smooth muscle neoplasms of the uterus that affect 25 % – 44 % of women in the reproductive age group and occur in over 70% of women by the onset of menopause (1).

#### 1.2.2 Types of uterine fibroids

##### 1.2.2.1 Magnetic resonance imaging (MRI) classification

The Funaki classification is the primary MRI classification system for uterine fibroids determining patient suitability for HIFU therapy (2). Funaki et al. classified uterine fibroids in 2007, based on the T2-signal intensity of the uterine fibroid compared to that of skeletal muscle, seen on a MRI scan (2).

It divides uterine fibroids into three groups.

- Funaki type I describes a uterine fibroid that is hypo-intense compared to skeletal muscle. It has a very low T2 signal.
- Funaki type II uterine fibroids are iso-intense to skeletal muscle, but the T2-signal intensity is lower than that of myometrium.

- Funaki type III describes a uterine fibroid that is hyper-intense. It has a higher T2- signal intensity compared to myometrium. These uterine fibroid types have poor HIFU therapy results due to hypervascularity (2).

#### 1.2.2.2 International Federation of Gynaecology and Obstetrics (FIGO) classification

FIGO uses a sub classification for uterine fibroids. The uterine fibroids are classified according to the location in the uterus. FIGO 0 ─ 2 is submucosal, FIGO 3 ─ 4 is intramural and FIGO 5 ─ 7 is subserosal. FIGO 8 describes a uterine fibroid in another place (3). It is important to determine both the FIGO and Funaki classifications of the uterine fibroids as studies have shown that uterine fibroids with high T2 signal intensity are difficult to treat and generally have a poor outcome (2).

### 1.2.3 Incidence and prevalence

Studies on racial differences in the prevalence and incidence of uterine fibroids have been done in the United States of America (USA). The incidence rates increased with age and the age standardized rates confirmed by ultrasound or on specimen analysis after hysterectomy, confirmed the incidence of 30.6 black woman per 1000, 8.9 white woman per 1000 and 8 Asian women per 1000 to have uterine fibroids (4). It is very difficult to estimate the exact prevalence of uterine fibroids in women. Many women are unaware of having uterine fibroids because they are not experiencing any symptoms and hence do not seek medical attention. The prevalence of uterine fibroids increases with age. In pre-menopausal women aged 35 to 39 years there is a clinical prevalence of 30% ─ 40% in African women and 10% ─ 15% in Caucasian women. In their late forties the prevalence of uterine fibroids increases to 50% in African women compared to 35% in Caucasian women (5).

### 1.2.4 Treatment of uterine fibroids

Patients with uterine fibroids may be asymptomatic (in up to 50% of cases) or can present with acute or chronic symptoms such as excessive uterine bleeding, abdominal pain, recurrent urinary tract infections and/or problems with fertility (6).

Treatment of symptomatic uterine fibroids can be achieved by taking pharmacological agents, undergoing surgery or by radiological intervention. Treatment depends on the patient's age, health, fibroid size, severity of symptoms and the need to maintain fertility or not (7–11).

Pharmacological agents do not remove the fibroid, but do improve the symptom profile and the patient's quality of life. Side effects of these agents and regrowth of the uterine fibroid usually limit their use and it is therefore used as a temporary treatment measure. It reduces the size of the fibroid and minimises the risk of bleeding when used as an adjuvant to surgery (12).

Hysterectomy used to be the most common treatment for uterine fibroids (13), but due to its long hospitalisation, post-operative complications and loss of the uterus (14), an increasing demand for non-invasive resolving techniques developed.

Less invasive techniques (such as laparoscopic myomectomy, uterine artery embolization (UAE), thermo-ablative treatments) (15), together with and high intensity focused ultrasound ( HIFU), a non-invasive technique, are becoming increasingly popular. These strategies allow for conservation of the uterus and have many advantages over open surgical procedures, including lower morbidity, shorter recovery and hospitalisation times and the use of sedation rather than a general anaesthesia (8,16,17).

Patients undergoing HIFU therapy can return to their normal daily activities within a day (16), compared to about 10 days after UAE and six weeks after myomectomy or hysterectomy (16,17). The introduction of HIFU in the treatment of uterine fibroids has expanded the options available for patients affected with symptomatic uterine fibroids (17). It can result in symptom relief for more than two years and only 10 % ─ 15% of the patients will require follow up treatments. (18)

## 1.3. High intensity focused ultrasound

### 1.3.1 History of ultrasound use and HIFU therapy

Energy carried in ultrasound waves can interact with human tissue. This has been recognised for many years, as early as the year 1927. The therapeutic use was recognised because of " the ability of ultrasound energy to cause a rise in tissue temperature that can lead to cell death" (6). Its earliest medical use was therapeutic rather than diagnostic. In the 1940's ultrasound was used to treat Parkinson's disease (19–21). Later in the 1990's, ophthalmology used ultrasound to treat raised intraocular pressure, glaucoma, retinal detachment, traumatic capsular tears and vitreous haemorrhage (22).

### 1.3.2 Physics and principles of HIFU

HIFU uses the physical effect of ultrasound on tissues. It raises the temperature of the targeted tissue above 60 °C for a second or longer to cause coagulative necrosis and immediate cell death. This increase in temperature is directly proportional to the power of the ultrasound beam passing through the tissue and the duration of exposure to the ultrasound beam. It will increase proportionally until a steady state is reached (23).

Ultrasound is generated by passing a current through a quartz piezoelectric crystal transducer. This results in ultrasound wave generation. The sound waves have a frequency between 0.5 to 10 MHz and can pass through "sonic mediums" which include all soft tissues, but not air or bone. Ultrasound can penetrate through tissue with only small amounts of energy being absorbed (19).

The acoustic pressure of the ultrasound wave causes mechanical vibrations resulting in tissue movement. Tissue movement again produces heat that is dissipated, because of the cooling effects of perfusion and conduction (6). Medical use of the energy carried in ultrasound occur when the high-energy beam is brought to a tight focus. This focused ultrasound was discovered by Grutz-Macher in 1935 by using a concave-shaped transducer to focus the ultrasound beams onto a distal target point (20). Energy levels of 100 up to 10 000 $W.cm^2$ can be generated without significant

heat loss along its path. A temperature gradient exists between the tissues at the focal point and the tissue surrounding it (6).

Tissue destruction at the focal point occurs by three mechanisms. Firstly, coagulation necrosis from the thermal effect. Protein denaturation occurs when the temperature is raised to more than 55$^{o}$ C at the target area. This results in coagulative necrosis and cell death, with the creation of a cigar-shaped lesion, in the direction of the ultrasound beam (24,25). Increasing the temperature higher than 60$^{o}$ C is undesirable as this will lead to less predictable ablation zones (23).

Secondly, the mechanical effects of the ultrasound results in cavitation formation (8,26,27). Cavitation is due to a mechanical effect produced by acoustic pulses, resulting from alternating compression and expansion of tissue as an ultrasound beam propagates through it (27,28). Furthermore it has been postulated that injury to the cell may generate apoptosis mediators that spread through gap junctions to the adjacent cells and result in tissue destruction (29).

### 1.3.3 Real-time monitoring of HIFU treatment

Ultrasound guided (USG) and magnetic resonance imaging (MRI) allows one to have real-time monitoring of therapy. It is needed during HIFU administration for accurate focal point targeting, monitoring of treatment effect and to minimise collateral damage. It is difficult to predict the exact temperature at the focal point, because of tissue inhomogeneities such as blood vessels, fat, muscle and the presence of gas or bone (30).

If ultrasound real-time monitoring is used, thermally induced grey-scale changes indicate temperature rise and hence tissue destruction. Available extracorporeal devices that are ultrasound assisted include the HAIFU System and the Chongqing HIFU Technology (25).

An alternative to HIFU ultrasound systems are MRI assisted devices. Machines that have MRI include Exablate 2000 and InSightec (25). They possess real-time thermal mapping and provides temperature data within seconds of HIFU exposure (23). The

MRI real-time monitoring method was introduced in 1993 by Hynynen and the first clinical trial looking at uterine fibroid response to HIFU therapy was done in 2003 by Tempany et al.(31). MRI-real time monitoring requires both a MRI-compatible HIFU machine and a MRI-compatible anaesthetic machine.

Temperature mapping allows detection of small temperature elevations before any irreversible tissue damage occurs (32). MRI has the advantage of high-resolution images, the ability to differentiate fine tumour detail and to see clear tumour boundaries. It is especially useful in obese patients, in whom USG imaging is difficult (29).

### 1.3.4 Delivery of HIFU

Extracorporeal or non-extracorporeal devices can be used to deliver HIFU. Extracorporeal devices are mainly used to treat readily accessible organs, such as breasts, cutaneous tissue, limbs, abdomen, and brain. Extracorporeal HIFU is guided by either USG or MRI. The general rule is that if there is a suitable acoustic window on the skin that allows uninterrupted (no air-filled viscus) propagation of the HIFU beam to the target organs, the use of extracorporeal HIFU can be used (33,34). These units are large machines operating at higher intensities and have their ultrasound beams delivered through an inbuilt water reservoir (6,35).

The water reservoir is devoid of air bubbles, to prevent deflection of ultrasound waves off them. The water is used as a medium for ultrasound waves to travel through. Patients going for HIFU treatment will have their skin (overlying the area of treatment) submerged into the water or will lie on a coupling medium such as gel pad.

Non-extracorporeal devices include transrectal, laparoscopic, interstitial, endoscopic and handheld probes (6,35).

### 1.3.5 Uses of HIFU

HIFU is often used in the treatment of benign and malignant solid tumours:

- hepatocellular carcinoma (HCC)
- prostate carcinoma and hyperplasia
- renal cell carcinoma (RCC)
- bladder tumours
- pancreatic cancer palliation
- obstetric and gynaecological procedures (uterine fibroids) (27)
- ablation for atrial fibrillation (36)
- glaucoma (37).

The following groups of disease profiles are still being investigated for suitability of treatment with HIFU:

- bone and breast neoplasia
- soft tissue sarcoma
- managing gastrointestinal haemorrhage
- thrombolysis
- ablating structural myocardial lesions (38).

### 1.3.6 Limitations to HIFU

Limitations to HIFU therapy can be divided into patient specific factors and USG machine factors. HIFU cannot be used for tumours in air-filled viscera, such as in the stomach, intestines and lungs. As bone and air absorb and deflect ultrasound it becomes difficult or even dangerous as treatment cannot be accurately planned or executed and collateral tissue damage may occur (25,39). Scattered and reflected high-intensity ultrasound waves may result in skin burns, peripheral nerve damage, and bowel injury (25,39).

Limitations secondary to USG real-time monitoring include artefacts, such as acoustic shadowing, reverberation and refraction. Other limiting factors are the distance of ultrasound penetrance, as well as the amount of energy absorbed by various tissues. Fibrotic, fatty, and highly vascularized tissues not only weaken, but

also absorb soundwave energy differently. This may result in an unpredictable distribution of cell death (25,35,39).

### 1.3.7 HIFU treatment of uterine fibroids

HIFU has been available for more than two decades (40), with the aim of reducing or eliminating the symptoms caused by uterine fibroids (41). Almost all types of uterine fibroids can be treated with HIFU therapy. One important factor is that the subserosal uterine myomas should not be closer than 15 mm to the serosal surface (of the uterus), as this can interfere with future pregnancies (42).

The patient is positioned prone with the acoustic pathway passing from the transducer through the water reservoir, on which the patient is positioned (6). The MRI images of the patient, that was done prior to the HIFU therapy, are opened on the workstation of the focused ultrasound therapy system. The HIFU operator then defines the fibroid volume needed to treat and directs high intensity focused ultrasound waves until the entire volume of the fibroid(s) is treated. The temperature reached inside the uterine tissue reaches temperatures of more than 60°C. High temperature destroys the tissue through a coagulative necrosis, cavitation induced necrosis and possibly apoptosis mediator induced cell death (8,17,23-29).

The system plans the individual sonifications and shows the pathway that each sonication will take. This is achieved by the transducer that can tilt, up to ± 20°, in all directions. All these pathways are carefully examined to ensure that no beams pass through any structures that ought to be avoided, e.g. the small bowel. The distance of the beam passing through the fibroid is checked as large neurovascular bundles lie behind the uterine fibroid. The neurovascular bundles are at risk of injury as some energy deposition can remain after the beam has passed through the fibroid (43) .

Once the patient is correctly positioned, the target volume defined and the HIFU treatment planned, verification sonifications are performed. Only when the HIFU operator is satisfied that the targeting is accurate, do they proceed with the treatment cycle (6). The treatment itself consists of repeated sonifications which then results in a large area of ablated tissue. Each sonification is short, usually lasting around 20

seconds and is monitored with thermal mapping (23,44). Sonifications are interleaved, allowing a cooling period of 90 seconds between sonifications. This sonification technique helps to minimize treatment time (23).

The Food and Drug Administration (FDA) has limited the maximum treatment time for HIFU to 3 hours (43,45). The theoretical risk of deep venous thrombosis formation secondary to prolonged immobilisation and patients' discomfort is the reason for this limitation. The 3 hour limitation excludes patient positioning and usually allows for 60-90 sonifications (23,43).

### 1.4. Demographics of patients undergoing HIFU therapy

Most of the literature identified on HIFU therapy for uterine fibroids originates from East Asia, the United States of America (USA) and Western Europe (47,49,67-69,71-73). Three studies from China (Cheng et al.,[47] Chen et al.,[49] Wang et al.[72]), two from the USA (Barnard et al.,[71] Jacoby et al.[69]) and three from Europe (Ikink et al.,[73] Ruhnke et al.[68] and Vaessen et al.[67]) is summarised in Table I and will be discussed. The two biggest, large scale studies identified were, multicentre, retrospective studies done in China consisting of 2604 (47) and 9988 (49) patients, respectively. The mean age of these patients was 40.4 (49) ─ 41.4 (47). Studies by Barnard et al.[71] and Jacoby et al.[69] reported a mean age of 44 years (69,71) and Ikink et al.,[73] Ruhnke et al.[68] and Vaessen et al.[67] a mean of 42.4(67) ─ 47 +/- 4 years (73,68).

Cheng et al.,[47] Chen et al.,[49] and Wang et al.[72] did not record the BMI of their patients. Barnard et al.[71] and Jacoby et al.[69] had BMI's of 25.6 ─ 27.4 kg/m (69,71) with Ruhnke et al.[68] and Vaessen et al.[67] recording BMI's of 22.5 ─ 23 +-3 kg/$m^2$ (67,68). The parity and gravity of the patients undergoing HIFU therapy in all the listed studies were not reported (47,49,67-69,71-73).

### 1.5. Characteristics of uterine fibroids treated

A study by Barnard et al. (71) and Ikink et al (73) had a predominance of multiple fibroids, being 56% (71) and 76% (73) respectively. However, only 12% of 9988 patients in the study by Chen et al. (49) had multiple fibroids. The median total fibroid volume recorded by Chen et al. (49), Wang et al. (72) and Ruhnke et al. (68) were

67.5 (49), 95 ─ 126.9 (72) and 124.9cm$^3$ (68). A study by Barnard et al. (71) recorded bigger total fibroid volumes of 249.2cm$^3$ as did Jacoby et al. (69), recording fibroid volumes of 217cm$^3$. Percentages of the types of uterine fibroids were similar in most of the studies, with intramural fibroids being most prevalent (49,68,72,73). The location of the fibroids was mentioned in only one of these studies (49), being predominantly on the anterior wall.

### 1.6 HIFU treatment for uterine fibroids

Chen et al. (49) recorded the shortest treatment times of 84.2 minutes. Longer treatment times were recorded by Barnard et al. (71), Jacoby et al. (69), Ruhnke et al. (68) and Vaessen et al. (67), being 390 ─ 405 (71), 228 (69), 244 (68) and 269 (67) minutes. It is important to take note that the treatment time was differently defined in the study by Chen et al. (49), where time was recorded from the first to the last sonification. However, in the other listed studies, treatment time was defined as the time from when the patient was put on the table to when treatment was completed. Cheng et al. (47), Chen et al. (49) and Jacoby et al (69) had median sonification times of 849-851 (47), 1243.8 (49) and 9180 (69) seconds. Ikink et al. (73), Ruhnke et al. (68) and Vaessen et al. (67) did not record their sonification times. Cheng et al. (47) and Wang et al (72) recorded energy used as 338 275 ─ 334 000 J (47) and 463 200 ─ 483 000 J (72), respectively. Barnard et al. (71), Jacoby et al. (69), Ikink et al. (73), Ruhnke et al. (68) and Vaessen et al (67) did not record their energy used.

### 1.7 Pain

The following aspects of pain will be discussed. The definition, classification, physiology and pain experienced during HIFU treatment.

#### 1.7.1 Definition of pain

International Association for Study of Pain (IASP) defines pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage” (58).

### 1.7.2 Classification of pain

#### 1.7.2.1 Pain can be classified as either acute or chronic.

Acute pain is defined as “pain of recent onset and probable limited duration. It usually has an identifiable temporal and causal relationship to injury or disease.” Whereas chronic pain “commonly persists beyond the time of healing of an injury” and frequently there may not be any clearly identifiable cause. It is defined as “pain lasting longer than 3months” (51).

#### 1.7.2.2 Pain can also be classified as either nociceptive or neuropathic.

Nociceptive pain is defined as “pain arising from activation of nociceptors.” Noxious perception results from cellular damage following surgical, traumatic, or disease related injuries. Neuropathic pain is defined by the international Association for the Study of Pain (IASP) as “pain initiated or caused by a pathologic lesion or dysfunction in peripheral nerves and the central nervous system.” (59).

In the acute pain setting, nociceptive pain typically predominates although patients may also experience neuropathic pain (60,61). Features in the pain history that may suggest a diagnosis of neuropathic pain include:

- procedures or interventions done where nerve injury is at high risk
- quality of pain can be described as an electric shock, burning, shooting or stabbing pain
- pain without a clear precipitating factor
- pain associated with regional autonomic features, such as colour changes, temperature changes and sweating
- dysaesthesia’s, allodynia and areas of hypoaesthesia’s (60,61).

#### 1.7.2.3 Nociceptive pain is further classified as either somatic or visceral.

Somatic pain may be described as “a sharp, hot or stinging, well localised pain. It is associated with local and surrounding tenderness.” In contrast to this, visceral pain may be described as “dull, cramping, or colicky pain. It is often poorly localised and may present with referred pain.” Symptoms such as nausea, sweating and cardiovascular changes can accompany this type of pain (62).

### 1.7.3 Physiology of pain

The perception of pain is an important protective mechanism that involves multiple interacting mechanisms between the peripheral and central nervous system (59).

#### 1.7.3.1 Peripheral nociceptors

Noxious stimuli are perceived by peripheral sensory organs (nociceptors) and transduced into an action potential for conduction to the central nervous system (59).

Conduction happens through nociceptive afferents which are widely distributed throughout the body. These afferent fibres are either medium-diameter lightly myelinated A-delta fibres, or small diameter, slow conducting, unmyelinated C-fibres. The C-fibre polymodal nociceptor is most abundant. They respond to physical or chemical stimuli. Physical stimuli include heat, cold and pressure.

Thermal sensation is detected by a range of transient receptor potential channels (TRP) (62).

#### 1.7.3.2 Transmission of pain in the spinal cord

The afferent pain fibres, both A-delta and C-fibres, have their cell bodies, in the dorsal root ganglia. These fibres innervate the trunk, limbs and viscera. The pain fibres innervating the head, oral cavity and neck are found in the trigeminal ganglia.

These afferent terminal cell bodies contain neurotransmitters that are released by different intensity stimuli (63). The release of the neurotransmitters, such as excitatory amino acids (glutamate and aspartate), peptides (substance P) and neurotrophic peptides activates α-amino-3-hydrox y-5-methyl-4-isoxazolepropionic acid (AMPA) receptors post-synaptically which rapidly signals information relating to the location and intensity of the noxious stimuli (64).

#### 1.7.3.3 Projecting pain to the central nervous system

Ascending pathways from the spinal cord to the midbrain, forebrain and cortex explains the different qualities of pain experienced (65).

The spinothalamic pathway ascends the primary afferent terminals to the dorsal horn ganglia, to the thalamus and then to the somatosensory cortex. This pathway provides information about the site and type of pain stimulus (65).

The spinoreticular and spinomesencephalic pathways project the pain afferents to the medulla and the brainstem, integrating pain information with homeostatic, autonomic and arousal responses. It also projects pain afferents to other central areas mediating emotional and the affective component of pain (65).

### 1.7.4 Type of pain experienced during HIFU therapy of uterine fibroids

From the classification of pain by the IASP, pain during HIFU can be summarised as acute pain, both nociceptive (somatic and visceral) and neuropathic.

#### 1.7.4.1 Nociceptive pain during HIFU

Pain during HIFU has both a somatic and visceral aspect to it.

**Somatic**

The exact reason why patients experience pain during and post HIFU therapy for uterine fibroids is not clear. The hypothesis is that the recommended delay between sonifications (that should be approximately 60–90s) was not adhered to, this may result in thermal build-up in the path of the ultrasound beam causing pain (27). The most common post-operative complication of HIFU therapy is local skin burns. This happens over the area where the patient was lying on the ultrasound transducer. The pain can be described as somatic nociceptive pain (46).

**Visceral pain**

Another possible reason for intraoperative pain is thermal damage of fibroid tissue resulting in local oedema inside the fibroid capsule. This causes a pressure rise within the fibroid sufficient to extend the fibroid beyond its lethal volume and can result in pelvic and abdominal pain. It is important to distinct between the different types of pain, as the likelihood of responding to analgesic strategies and the prediction of the duration of pain varies.

### 1.7.5 Pain assessment using single dimensional pain scales in HIFU therapy

Pain scores, using either a 4-, 10- or 100-point pain scale were recorded in the studies by Cheng et al. (47), Barnard et al. (71) and Ruhnke et al (68). All the patients in the study by Cheng et al (47), had a pain score of <4/10 during the procedure. Barnard et al. (71) had a post-procedural pain score of 38-48/100 and Ruhnke et al. (68) measured pain using a 4-point pain scale before, during and after HIFU therapy, where the mean intraoperative pain score was 1.2/4 with 39% of the patients never complaining about pain at all.

### 1.7.6 Pain management and anaesthetic techniques in HIFU therapy

Minimal sedation and analgesia were administered to the patients in the studies done by Wang et al. (72), Barnard et al. (71), Jacoby et al. (69), Ikink et al. (73) and Ruhnke et al. (68). All these patients appeared to tolerate the procedure well.

Cheng et al. (47), Chen et al. (49), Wang et al. (72), Barnard et al. (71), and Jacoby et al. (69) administered intravenous (IV) fentanyl and midazolam to all their patients. Ikink et al. (73) and Ruhnke et al. (68) used IV paracetamol and NSAID's. Oral diazepam drops were administered to the patients in the Ruhnke et al. (68) study, but only when they requested it. Vaessen et al. (67), studied the sedation technique for HIFU therapy. This was the only identified anaesthetic related HIFU study. Conscious sedation with multimodal analgesia was administered consisting of oral oxycodone 5mg, 1g IV paracetamol, 75mg IV diclofenac and an infusion of propofol/ketamine (mean dose 1309mg/39.5mg, respectively).

Lastly, studies have completed HIFU therapy in highly compliant patients without giving any analgesia or sedation (34,35). The first study was done between March – August 2009 in China (35) and the second in 2016 in Italy (34).

Table I gives a summary of the differences, in the listed studies, regarding their demographics, uterine characteristics, HIFU treatment and intraoperative sedation and analgesia given.

## Table I: Differences in the demographics, uterine characteristics, HIFU treatment and intraoperative sedation and analgesia given

| | This CHBAH study | China | United States of America | Europe |
|---|---|---|---|---|
| Year the study was done | 2017 | 2010-2013 (47)<br>2006-2007 (49)<br>2012-2013 (72) | 2010-2011 (71)<br>2011-2012 (69) | 2010-2013 (73)<br>2012 (68)<br>2013-2014 (67) |
| Year the study was published | | 2015 (47), 2015 (49),<br>2018 (72) | 2016(71)<br>2015(69) | 2014 (73), 2013 (68)<br>2017 (67) |
| Number of patients enrolled/ number of patients treated for uterine fibroids | 236 / 223 | 2604 / 1663 (47)<br>9988 / 7439 (49)<br>94/ 94 (72) | 91 / 43 (71)<br>35 / 20 (69) | 119 / 51 (73)<br>18 / 18 (68)<br>20/ 20 (67) |
| **Demographics** | | | | |
| Age | 35.1 | 41.4 +/- 5.2 (47)<br>40.4 +/- 5.8 (49)<br>38.6 – 41.6 (72) | 44.0 (71)<br>44.0 (69) | 46 (73)<br>47 +/- 4 (68)<br>42.4 (67) |
| BMI | 25.6 | | 26.7-27.4(71)<br>25.6(69) | 23 +/-3 (68)<br>22.5 (67) |
| Parity/gravidity (% nulliparous) | 71.5 | | | |
| **Uterine fibroid characteristics** | | | | |
| % single/multiple fibroids | 34.7 / 65.3 | 88 / 11 (49) | 44/56 (71) | 24/76 (73) |
| Total fibroid volume ($cm^3$) | 164.4 | 67.5 (49),<br>95 – 126.9 (72) | 225.0-249.2 (71)<br>217 (69) | 273 (73)<br>124.9 +/- 139.88 (68) |
| ***Types of fibroids (%)*** | | | | |
| Submucosal | 11.3 | 12 (49), 1.3 – 2.3 (72) | | 16 (73) / 22 (68) |
| Intramural | 63.0 | 68 (49), 50 – 77.9 (72) | | 59 (73) / 63 (68) |
| Subserosal | 25.7 | 20 (49), 8.8 – 47.7 (72) | | 25 (73) / 15 (68) |
| ***Location of fibroids*** | | | | |
| Anterior wall | 33 | 47 (49) | | |
| Posterior wall | 28 | 31 (49) | | |
| Lateral wall | 21 | 6 (49) | | |
| Fundus | 18 | 16 (49) | | |
| **Treatment variables** | | | | |
| Treatment duration (minutes) | 144.3 | 84.2 +/- 38.8 (49)<br>114.4 – 174.5 (72) | 390 – 405 (71)<br>228 (69) | 120 – 180 (73)<br>244 +/- 45 (68)<br>269 (67) |
| Sonification time (seconds) | 687.7 | 1243.8 +/- 725.2(49)<br>849 – 851 (47) | 9180 (69) | |
| Power (W) | 381 | 350 – 400 (47) | | |
| Energy used (Joules) | 265 000.0 | 338 275 – 334 000 (47)<br>463 200 – 483 000 (72) | | |
| **Intraoperative sedation and analgesia given** | Conscious sedation: using an average of 5 different classes of drugs, 1 for sedation and 4 addressed pain | Conscious sedation: IV fentanyl 50 – 400ug (47), 0.8 – 1.0ug/kg (2,3), IV midazolam 1 – 4mg IV (47), midazolam 0.02 – 0.03mg/kg (2,3) | Conscious sedation (71) IV fentanyl boluses (25 – 100ug) and IV midazolam (0.5 – 1.0mg) (69) | 1g IV paracetamol and IV diclofenac 75mg (73) or oral ibuprofen 400mg (68) (with oral diazepam drops on request (68))<br>Pre-medication * Ketamine and propofol infusion (67) |

* Premedicated with 1g IV paracetamol, IV diclofenac 75mg and 5mg oxycodone orally (67)

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## Section 2: Author's guidelines

This article in this research report is submitted in a format for publication in the Southern African Journal of Anaesthesia and Analgesia (SAJAA). Below are the author guidelines for submission taken directly from SAJAA. The article will follow these guidelines.

### Southern African Journal of Anaesthesia and Analgesia

### Authors guidelines

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2. Polgreen PM, Diekema DJ, Vandeberg J, Wiblin RT, Chen YY, David S, et al. Risk factors for groin wound infection after femoral artery catheterization: a case-control study. Infect Control Hosp Epidemiol [Internet]. 2006 Jan [cited 2007 Jan 5];27(1):34-7. Available from: http://www.journals.uchicago.edu/ICHE/journal/issues/v27n1/2004069/2004069.web.pdf.

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## Section 3: Draft article

# Uterine fibroid characteristics and intraoperative analgesic requirements during high intensity focused ultrasound therapy at a central hospital

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**Keywords**

High intensity focused ultrasound (HIFU), uterine fibroid therapy, intraoperative analgesia for HIFU therapy, analgesia for uterine fibroid therapy

**Abstract**

**Background**

Uterine fibroids affect 25% ─ 44 % of women of reproductive age. High intensity focused ultrasound (HIFU) is a non-invasive treatment for fibroids, that is becoming increasingly popular as it has many advantages over surgical procedures. The clinical impression at Chris Hani Baragwanath Academic Hospital (CHBAH) is that HIFU therapy for fibroids is very painful.

**Methods**

A retrospective, contextual and descriptive study was done reviewing all HIFU records (n=236) at CHBAH from 13 October 2015 to 30 September 2017.

**Results**

Of the anaesthetic charts, 223 (94.5%) were available for analysis. Having multiple fibroids increased (p=0.002) the likelihood of requiring higher dosages of short-acting opioids. An increase in treatment time had a high likelihood of resulting in an increase in both short- (p=0.004) and long-acting (p=0.001) opioid requirements and an increase in energy used had a high likelihood of increasing long-acting opioid (p=0.002) requirements. Body mass index (BMI) influenced intraoperative analgesic requirements. Patients who had a normal BMI were likely to require less intraoperative analgesic drugs than those who were overweight and obese.

**Conclusions**

Most of the patients presenting at CHBAH for HIFU therapy have multiple fibroids and judging by the of intraoperative analgesia administered, HIFU treatment appears to be very painful, which is not in keeping with most other studies.

**Introduction**

Uterine fibroids are benign smooth muscle neoplasms of the uterus that affect 25% ─ 44 % of women of reproductive age.[1,2] They can either be asymptomatic (in up to 50% of cases) or they can present with acute or chronic symptoms such as excessive uterine bleeding, abdominal pain, recurrent urinary tract infections and/or problems with fertility.[3]

Treatment of symptomatic uterine fibroids can be accomplished by taking pharmacological agents, undergoing surgery or by radiological intervention. Treatment depends on the patient's age, health, fibroid size, severity of symptoms and the need to maintain fertility or not.[4-8] Hysterectomy was previously the most common treatment for uterine fibroids,[9,10] but due to prolonged hospitalisation, postoperative complications and loss of the uterus, an increasing demand for less invasive techniques developed. [11]

Less invasive techniques (such as laparoscopic myomectomy, uterine artery embolization (UAE) and thermo-ablative treatments),[12] together with high intensity focused ultrasound (HIFU), a non-invasive technique, are becoming increasingly popular. These strategies allow for conservation of the uterus and have many advantages over open surgical procedures including, but not limited to, lower morbidity, faster recovery, shorter hospital stay and permits the use of sedation rather than a general anaesthesia.[5,13,14] Since 1927 ultrasound has been increasingly used in the medical field.[3] HIFU uses the physical effect of ultrasound on tissues. It raises and maintains the temperature of an isolated part of the tissue to above 60 °C for a second or longer, which causes coagulative necrosis, immediate cell death[15] and aims to reduce or eliminate the symptoms caused by uterine fibroids.[16]

Several studies used a single dimensional pain scale to rate the intensity of pain during uterine fibroid HIFU therapy.[3,6,20,26,27,32,33] Five studies[6,20,27,32,33] had similar results using the visual analogue pain score. In none of these studies was a score of more, than 5 (out of 10) reported at any given point during HIFU therapy.

In contrast to the pain experienced during HIFU therapy in previous studies, the clinical impression at Chris Hani Baragwanath Hospital (CHBAH) is that HIFU therapy for uterine fibroids is very painful. It is possible that the demographics of our population and the uterine fibroid characteristics treated at CHBAH can explain this difference. The aim of the study is to describe the uterine fibroid characteristics and the intraoperative analgesic requirements of patients undergoing HIFU therapy at CHBAH.

**Methods**

A retrospective, contextual, descriptive research design was followed in this study. Approval to conduct this study was obtained from the Human Research Ethics Committee (Medical) of the University of the Witwatersrand and other relevant authorities.

The study population consisted of the records of all patients who have undergone HIFU therapy at CHBAH, from inception on 13 October 2015 to 30 September 2017. Missing and illegible anaesthetic records were excluded.

The data collection sheet (Microsoft Excel™ spreadsheet) was drafted after reviewing the literature, thereby ensuring content validity. It was reviewed by the head of the HIFU unit as well as a senior anaesthetist with experience in HIFU sedation thereby, ensuring content and face validity. The data collection sheet included the following information: patient demographics, uterine fibroid characteristics, HIFU therapy and intraoperative sedation and analgesic requirements. Once the relevant approvals had been received, data were collected by one author (AF) from the electronic HIFU records and pre-printed anaesthetic records.

Data were analysed in consultation with a biostatistician using STATA® version 14.1. Categorical variables were analysed using frequencies and percentages. Numerical variables were analysed using means and standard deviations or medians and interquartile ranges depending on the distribution of the data. A univariate logistic regression model was used to determine correlations between both short- and long-acting opioids (dose per kilogram administered) and six variables. A p-value of $<0.05$ was considered as statistically significant.

The HIFU unit at CHBAH, for uterine fibroid therapy, was the first in Africa. A standard preoperative assessment is done for suitable HIFU candidates and a pre-treatment magnetic resonance imaging (MRI) is ordered. The location, number, diameter and volume of fibroids and abdominal wall thickness are recorded from the MRI. A urinary catheter is inserted before therapy is commenced, as it may be needed, intraoperatively to fill the bladder, to improve the field of vision by pushing small bowel out of the way.[15] The patient is positioned prone. All the sonification pathways are carefully examined to ensure that no beams pass through any structures

that ought to be avoided for example the small bowel. The depth of the beam passing through the fibroid is checked as neurovascular bundles, behind the fibroids, are at risk of injury. Should the beam reach the neurovascular bundle, this will present as a sharp pain radiating down the leg.[18] Focused ultrasound waves are directed repeatedly, until the entire volume of the fibroid(s) is treated.

HIFU treatment at CHBAH is performed in the radiology suite with the added risk of anaesthesia in a remote location. Patients are counselled extensively about the need to lie still during HIFU therapy. An emergency button is provided to the patient and it is explained that the patient should press the button when they experience discomfort or pain. The alarm will cause the HIFU operator to stop treatment and reassess the directions of the focused beams.

The anaesthetic protocol with sedation and multi-modal analgesia is used. A short-acting benzodiazepine (midazolam) is used for sedation, starting at a low dose and aiming to reach a modified Ramsey sedation score of 2. Intraoperative analgesia includes:

- 1 gram of intravenous (IV) paracetamol
- non-steroidal anti-inflammatories (NSAID's), if there is no contra-indication to it,
- IV morphine boluses (50 ug/kg), titrated up to a total of 100 ug/kg IV
- IV fentanyl boluses, given in increments of 25 ug/ml to a maximum of 200 ug IV
- and 100 ug IV alfentanil boluses are given for periods of intense pain.

Recovery from sedation occurs in the HIFU unit. The Modified Aldrete scoring discharge criteria applies to patients that have undergone HIFU therapy. Patients are admitted to the ward overnight and followed up post-operatively to assess hemodynamic stability, possible complications and level of pain.

**Results**

This study included 236 records of patient who had undergone HIFU therapy at CHBAH between 13 October 2015 to 30 September 2017. The anaesthetic charts of 223 (94.5%) patients were available for analysis. The demographic characteristics of the patients (n=236) are summarised in Table I. There were no significant differences between patients with single and multiple fibroids. The parity and gravidity were recorded in 228 patients of which 117 (51.3%) have never been pregnant and 163 (71.5%) have never delivered a baby. Two

hundred and thirty-three (98.7%) of the patients treated where black. Of the 236 patients, 154 (65.3%) had multiple fibroids. There are missing data points in all the demographic data, as can be seen in Table I.

**Table I: Demographic characteristics of patients**

| | **All patients (n=236)** | | **Patients with single fibroids (n=82)** | | **Patients with multiple fibroids (n=154)** | | |
|---|---|---|---|---|---|---|---|
| **Variable** | n (missing data points) | Mean (SD) | n | Mean (SD) | N | Mean (SD) | p-value |
| **Age (yrs)** | 235 (1) | 35.1 (5.7) | 82 | 33.6 (6.4) | 153 | 35.8 (5.1) | 0.15 |
| **Height (m)** | 189 (47) | 1.6 (6.8) | 63 | 1.6 (6.8) | 126 | 1.6 (6.8) | 1.00 |
| **Weight (kg)** | 228 (8) | 67.7 (25.6) | 81 | 67.1 (13.2) | 147 | 68.1 (12.8) | 0.65 |
| **BMI ($kg/m^2$)** | 183 (53) | 25.6 (5.1) | 62 | 25.5 (5.5) | 121 | 25.7 (4.9) | 0.85 |

The type of fibroids is shown in Table II, with intramural fibroids being more frequent in both the single and multiple fibroid groups.

**Table II: Type of fibroids**

| Type of fibroid | All fibroids (n=576) | | Number of single fibroids (n=82) | | Number of multiple fibroids (n=494) | |
|---|---|---|---|---|---|---|
| | n | % | n | % | n | % |
| **Submucosal** | 65 | 11.3 | 15 | 18.3 | 50 | 10.1 |
| **Subserosal** | 148 | 25.7 | 21 | 25.6 | 127 | 25.7 |
| **Intramural** | 363 | 63.0 | 46 | 56.1 | 317 | 64.2 |
| **Total** | 576 | 100 | 82 | 100 | 494 | 100 |

The location of 506 (87.8%) of the 576 fibroids treated was documented. One hundred and twenty-four (24.5%) were on the anterior wall, 161 (31.8%) on the posterior wall, 124 (24.5%) on the lateral wall, 91 (18.0%) were fundal and 6 (1.2%) fibroids were in other locations in the uterus. Table III summarises the measurements of the fibroids. Although the single fibroid's median longitudinal, left-right, anterior-posterior measurements and the volume per fibroid were larger, the total fibroid volume was larger in the multiple fibroid group.

Table III summarises the measurements of the fibroids. Although the single fibroid's median longitudinal, left-right, anterior-posterior measurements and the volume per fibroid were larger, the total fibroid volume was larger in the multiple fibroid group.

**Table III: Measurements of fibroids**

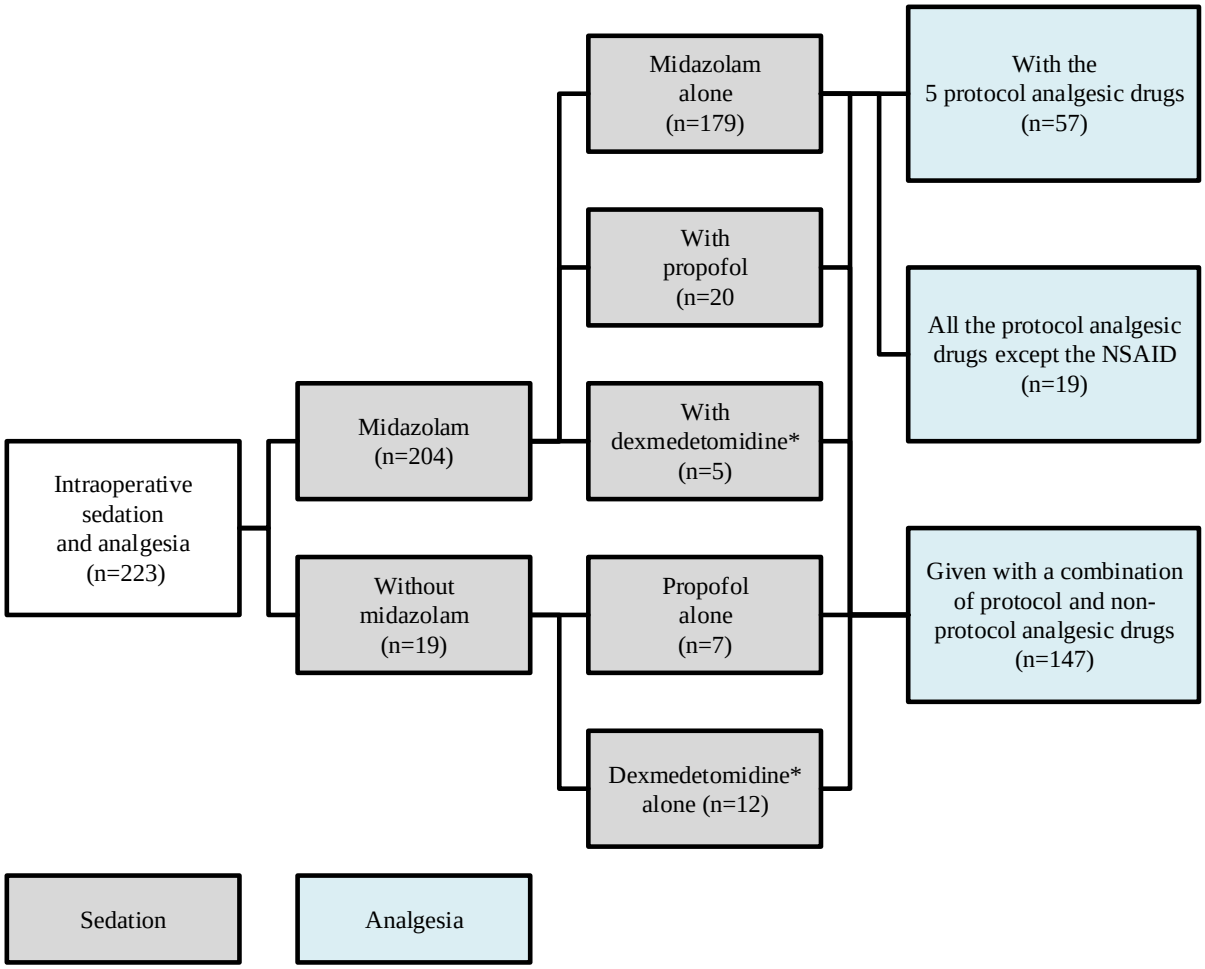
| Measurement | All fibroids (n=576) | Single fibroids (n=82) | Multiple fibroids (n=494) | p-value |
|---|---|---|---|---|
| **Longitudinal (mm)** | | | | |
| Median | 45.5 | 62.2 | 45.0 | |
| IQR | 33.0 ─ 64.0 | 39.5 ─ 89.0 | 32.8 ─ 59.5 | 0.34 |
| Range | 15.0 ─ 143.5 | 17.0 ─ 143.5 | 15.0 ─ 143.0 | |
| **Left-right (mm)** | | | | |
| Median | 41.4 | 56.9 | 40.0 | |
| IQR | 31.3 ─ 58.0 | 38.0 ─ 86.0 | 30.1 ─ 55.0 | 0.15 |
| Range | 11.7 ─ 163.2 | 15.0 ─ 163.2 | 11.7 ─ 152.2 | |
| **Anterior-posterior (mm)** | | | | |
| Median | 40.0 | 51.6 | 38.9 | |
| IQR | 29.0 ─ 54.0 | 36.6 ─ 74.0 | 28.4 ─ 50.6 | 0.33 |
| Range | 13.1 ─ 109.5 | 17.0 ─ 100.0 | 13.1 ─ 109.5 | |
| **Volume per fibroid ($cm^3$)** | | | | |
| Median | 39.3 | 99.5 | 36.1 | |
| IQR | 16.4 ─ 98.9 | 29.0 ─337.7 | 15.57 ─ 81.9 | 0.08 |
| Range | 1.5 ─ 1220.1 | 2.3 ─ 1109.1 | 1.5 ─ 1220.1 | |
| **Total fibroid volume ($cm^3$)** | | | | |
| Median | 164.4 | 99.5 | 185.4 | |
| IQR | 61.2 ─ 337.7 | 29.0 ─ 337.7 | 85.7 ─ 324.9 | 0.90 |
| Range | 2.3 ─ 1326.1 | 2.3 ─ 1109.1 | 1.5 ─ 1220.1 | |

The HIFU treatment variables are shown in Table IV. Higher maximum power of HIFU therapy was utilized for patients with multiple fibroids compared to those with single fibroids (p=0.002). Treatment time, sonification time and total energy used were higher among patients with multiple fibroids than among those with single fibroids, although these were not statistically significant. There were missing data points as can be seen in Table IV.

**Table IV: Treatment variables**

| Variable | All fibroids (n=236) | | Patients with single fibroids (n=82) | | Patients with multiple fibroids (n=154) | | |
|---|---|---|---|---|---|---|---|
| | n | Median (IQR) | n | Median (IQR) | n | Median (IQR) | p-value |
| **Maximum power (W)** | 234 | 400.0 (400 ─ 400) | 82 | 387.8 (350 ─ 400) | 152 | 396.0 (350 ─ 400) | 0.002 |
| **Minimum power (W)** | 234 | 322.0 (300 ─ 350) | 82 | 329.7 (325 ─ 350) | 152 | 317.5 (300 ─ 350) | 0.392 |
| **Average (W)** | 233 | 381.0 (381 ─ 399) | 82 | 376.2 (350 ─ 399) | 151 | 383.7 (381 ─ 399) | 0.175 |
| **Treatment time (minutes)** | 229 | 144.3 (120 ─ 195) | 82 | 120.2 (87 ─ 149) | 147 | 157.7 (120 ─ 195) | 0.169 |
| **Total sonification time (seconds)** | 232 | 687.7 (503 ─ 1001) | 82 | 531.2 (262 ─ 705) | 150 | 766.1 (503 ─ 1001) | 0.529 |
| **Total energy used (J)** | 232 | 265 000.0 (187 900 ─ 280 950) | 82 | 204 989.6 (94 550 ─ 280 950) | 150 | 292 915.0 (174 200 ─ 361 500) | 0.372 |

Figure 1 shows that 57 (25.6%) patients received all 6 of the protocol drugs. Conscious sedation and analgesia were administered by the anaesthetist using an average of 5 different classes of drugs per patient, with 4 of these drug classes addressed intraoperative pain. Midazolam, as sedation, was given to 204 (91.5%) patients, at a mean dose of 2.8 mg (SD=1.7) intravenously for multiple fibroids and 2.1 mg (SD=1.3) for single fibroids.




***** having both sedative and analgesic properties

**Figure 1: Intraoperative sedation and analgesia**

Figure 2 shows the different classes of analgesic drugs used by anaethetists and the number of patients they were administered to. The number of patients who received short-acting opioids adds up to more than the total number of patients (n=223), as patients often received combinations of short-acting opioids.

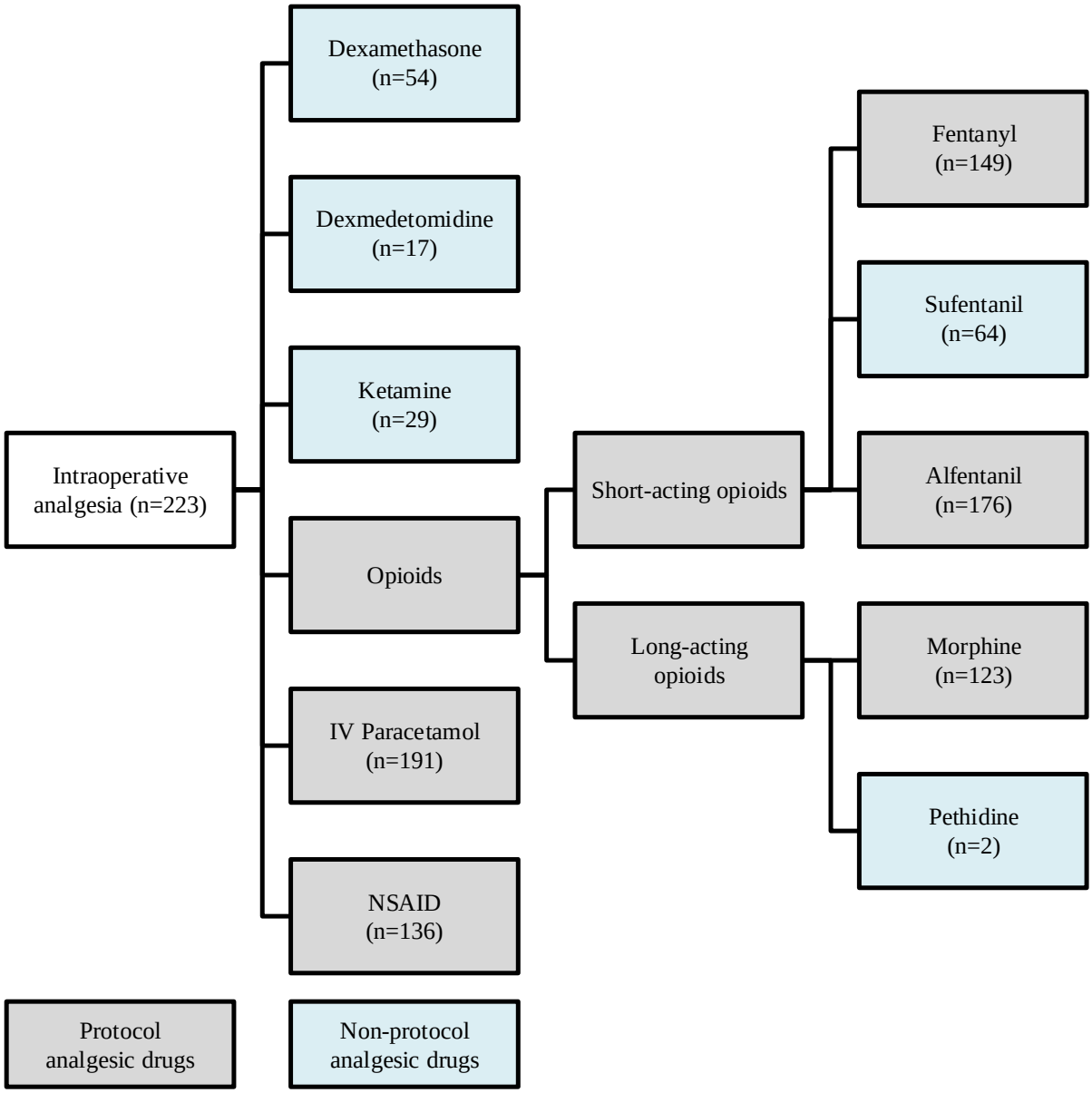



**Figure 2: Intraoperative analgesia**

Figure 3 shows the number of patients who received short-acting opioids. Fentanyl combined with alfentanil boluses were the most common combination of short-acting opioids used in 114 (51.1%) patients, with fentanyl given at a mean dose of 161.1 ug (SD=96.2) or 2.5 ug/kg. Alfentanil was given at a mean dose of 1187.2 ug (SD=1061.0) or 18.4 ug/kg. Sufentanil was given at a mean dose of 16.0 ug (SD=11.8) or 0.2 ug/kg. All the patients, except 2 (0.89%) required short-acting opioids for pain relief.

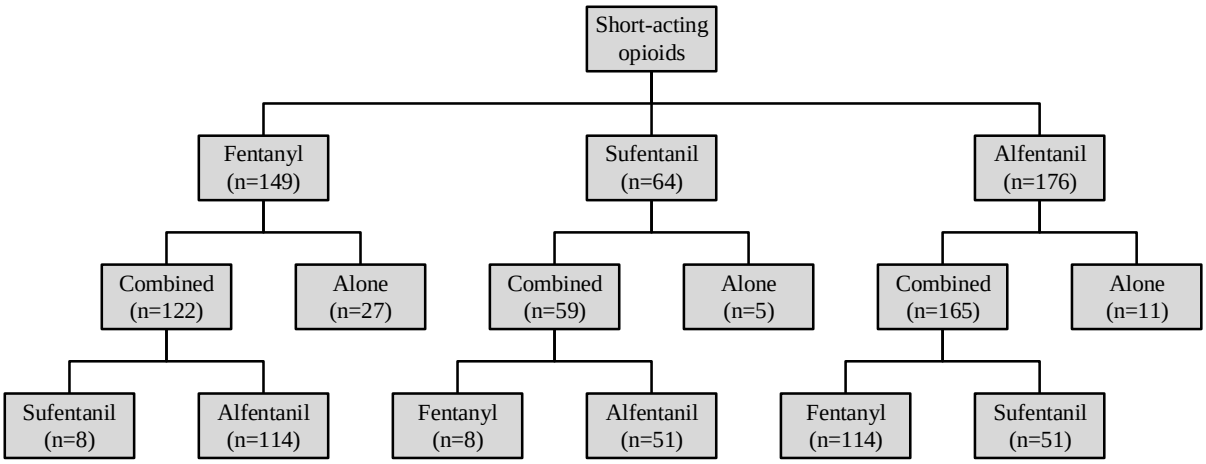



**Figure 3: Short-acting opioids**

Six patients (2.7%) received sedation and a single analgesic agent only. Of the 6 patients, 2 procedures were abandoned due to technical difficulties, 2 patients had short treatment times (18 and 69 minutes) and another 2 had low energy usage (2100 and 14000 J). The treatment time and energy usage of these patients above was well below the median treatment time (144.3 minutes) and median energy usage (265 000 J) of the study sample. A difference was observed between ketamine dosages used for single and multiple fibroids, higher dosages (21.4 mg, SD=13.5) were given to patients with single fibroids compared to patients with multiple fibroids (14.4 mg, SD=7.2).

Table V shows both the mean dose and the dose per kilogram of both the short and long-acting opioids. Fentanyl, sufentanil and alfentanil dosages were higher in patients with multiple fibroids than those with single fibroids. Not all the patients had weights documented and therefor dose per kilogram could not be calculated.

**Table V: Short- and long-acting opioids**

| | All fibroids | | | | Patients with single fibroids (n=82) | | | | Patients with multiple fibroids (n=154) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean dose per patient | | Dose per kilogram | | Mean dose per patient | | Dose per kilogram | | Mean dose per patient | | Dose per kilogram | |
| **Short-acting opioids** | **n** | **(ug)** | **n** | **(ug/kg)** | **n** | **(ug)** | **n** | **(ug/kg)** | **n** | **(ug)** | **n** | **(ug/kg)** |
| Fentanyl | 149 | 161.1 | 145 | 2.5 | 58 | 144.5 | 58 | 2.2 | 91 | 171.8 | 87 | 2.7 |
| Sufentanil | 64 | 16.0 | 63 | 0.2 | 20 | 11.5 | 20 | 0.2 | 44 | 17.0 | 43 | 0.3 |
| Alfentanil | 176 | 1187.2 | 172 | 18.4 | 57 | 970.2 | 57 | 15.3 | 119 | 1 299.6 | 115 | 19.9 |
| **Long-acting opioids** | **n** | **(mg)** | **n** | **(mg/kg)** | **n** | **(mg)** | **n** | **(mg/kg)** | **n** | **(mg)** | **n** | **(mg/kg)** |
| Morphine | 123 | 6.3 | 120 | 0.1 | 38 | 5.8 | 38 | 0.1 | 85 | 6.6 | 82 | 0.1 |

Univariate regression analysis was used to determine factors associated with intraoperative analgesic requirements. This analysis described the relationship between both short-acting and long-acting opioid (dose per kilogram) administered intraoperatively and 6 independent variables, sonification time, treatment time, fibroid volume treated, energy used, diagnosis of multiple fibroids and BMI. The results of this analysis are shown in Table IV. Zero was recorded when a fentanyl dose of 2.49 ug/kg or lower was administered (below average) and 1 when a dosage of 2.50 ug/kg and higher (above average) was administered. The cut-off point was determined by the mean fentanyl dose per kilogram which was 2.50 ug/kg, for all fibroids. The same applied to morphine, with an average dose per kilogram of 0.10 mg/kg.

**Table VI: Short- and long-acting opioids and the six independent variables**

| | **Short-acting opioid dose per kilogram Fentanyl (ug/kg)** | | **Long-acting opioid dose per kilogram Morphine (mg/kg)** | | **C.I** | | **Diff odds ratio** |
|---|---|---|---|---|---|---|---|
| Variable | Odds ratio | p-value | Odds ratio | p-value | | | |
| Sonification time (seconds) | 1.4 | 0.346 | 2.1 | 0.099 | 0.9 | 4.9 | -0.7 |
| Treatment time (minutes) | 2.8 | 0.004 | 4.2 | 0.001 | 1.8 | 10.2 | -1.5 |
| Fibroid volume ($mm^3$) | 0.7 | 0.508 | 1.4 | 0.688 | 0.3 | 5.9 | -0.7 |
| Energy (J) | 1.2 | 0.614 | 2.2 | 0.004 | 0.9 | 5.2 | -1.0 |
| Diagnosis (Multiple fibroids) | 3.2 | 0.002 | 1.1 | 0.857 | 0.4 | 2.6 | +2.1 |
| BMI ($kg/m^2$) | | | | | | | |
| 18.50-24.99 $kg/m^2$ | 0.9 | 0.950 | 0.2 | 0.239 | 0.02 | 2.7 | +0.7 |
| ≥ 25 $kg/m^2$ | 1.9 | 0.487 | 0.3 | 0.305 | 0.02 | 3.3 | +1.6 |
| ≥ 30 $kg/m^2$ | 2.0 | 0.477 | 0.5 | 0.597 | 0.04 | 6.6 | +1.5 |

Figure 4 illustrates the results of Table VI. An increase in treatment time has a high likelihood of resulting in an increase in both short- and long-acting opioid requirements. An increase in energy usage has a high likelihood of increasing long-acting opioid requirements and having multiple fibroids increases the likelihood of higher short-acting opioid requirements. BMI results provided insight into the intraoperative analgesic requirements during HIFU therapy. Patients who had a normal BMI, as defined by the WHO, were likely to need less intraoperative analgesic requirements, while those who were overweight and obese were twice as likely to require both short-acting and long-acting opioids.

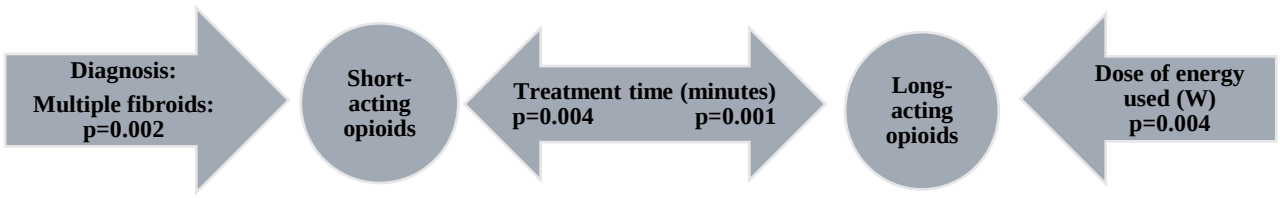



**Figure 4: Independent variables influence on short- and long-acting opioid requirements**

**Discussion**

HIFU therapy for treatment of uterine fibroids is becoming increasingly popular, having many advantages over open surgical procedures including, but not limited to, lower morbidity, faster recovery and shorter hospital stay.[15-17] It is imperative that the anaesthetic techniques, perioperative analgesic management and the anaesthetists' knowledge of HIFU therapy should evolve. Knowledge of the variables such as the diagnosis of multiple fibroids, treatment time, energy used, BMI and how these affect intraoperative analgesic requirements may guide the anaesthetist's plan for perioperative pain management. This knowledge is important for patient comfort during the procedure, as they are required to lie still for extended periods of time. General anaesthesia is not an option because of the risk of neurovascular injury.

Most of the literature identified on HIFU therapy for uterine fibroids originates from East Asia, the United States of America (USA) and Western Europe.[20-27] Three studies from China (Cheng et al.,[20] Chen et al.,[21] Wang et al.[22]), two from the USA (Barnard et al.,[23] Jacoby et al.[24] ) and three from Europe (Ikink et al.,[25] Ruhnke et al.,[26] Vaessen et al.[27]) are discussed in relation to results of this CHBAH study. In this study 65.3% of patients had multiple fibroids. A study by Barnard et al.[23] and Ikink et al.[25] also had a predominance of multiple fibroids, being 56%[23] and 76%[25] respectively. However, only 12% of 9988 patients in a multicentre, retrospective study done by Chen et al.[21] had multiple fibroids. The CHBAH sample had a median total fibroid volume of 164.4cm$^3$, this was bigger than those recorded by Chen et al.,[21] Wang et al.[22] and Ruhnke et al.[26] which had total fibroid volumes of 67.5,[21] 95 ─ 126.9,[22] and 124.9cm$^3$,[26] respectively. Bigger total fibroid volumes were reported by Barnard et al. (249.2cm$^3$)[23] and Jacoby et al. (217cm$^3$).[24]

In this study the median treatment time was 144.3 minutes, the sonification time 687.7 seconds and energy used 265 000 J. Longer treatment durations were recorded by Barnard et al.,[23] Jacoby et al.,[24] Ruhnke et al.[26] and Vaessen et al.[27] (390 ─ 405,[23] 228[24], 244 [26] and 269 [27] minutes). Chen et al.[21] recorded shorter treatment times of 84.2 minutes. It is important to take note that the treatment time was differently defined by Chen et al.[21], where time was recorded from the first to the last sonification. However, in the other studies, including this CHBAH study, treatment time was defined as the time from when the patient was put on the table to when treatment was completed. Cheng et al.,[20] Chen et al.[21] and Jacoby et al.[24] had median sonification times that were longer (849-851,[20] 1243.8[21] and 9180[24] seconds). Ikink et al.,[25] Ruhnke et al.[26] and Vaessen et al.[27] did not record their

sonification times. Cheng et al.[20] and Wang et al.[22] used higher energy during HIFU therapy (338 275 ─ 334 000J[20]and 463 200 ─ 483 000 J,[22] respectively). Barnard et al.,[23] Jacoby et al.,[24] Ikink et al.,[25] Ruhnke et al.[26] and Vaessen et al.[27] did not recorded their energy used.

The clinical impression at CHBAH is that HIFU therapy for uterine fibroids is very painful. Pain assessments such as VAS scores were not done and pain was therefore not quantified. Minimal sedation and analgesia were administered to the patients in the studies by Chen et al.,[21] Wang et al.,[22] Barnard et al.,[23] Jacoby et al.,[24] Ikink et al.[25] and Ruhnke et al.,[26] but these patients appeared to tolerate the procedure well. Pain scores, using either a 4, 10- or 100-point pain scale were recorded in the studies done by Cheng et al.,[20] Barnard et al.[23] and Ruhnke et al.[26] All the patients in the study by Cheng et al.[20] had a pain score of <4/10 during the procedure. Barnard et al.[23] had a post-procedural pain score of 38-48/100 and Ruhnke et al.[26] measured pain using a 4-point pain scale before, during and after the HIFU therapy, where the mean intraoperative pain score was 1.2/4 with 39% of the patients never complaining about pain at all.

In this CHBAH study an average of five different classes of drugs were administered, one for sedation (midazolam was administered to 91.5% of patients) and four of these drug classes addressed pain. Cheng et al.,[20] Chen et al.,[21] Wang et al.,[22] Barnard et al.[23] and Jacoby et al.[24] administered IV fentanyl and midazolam to all their patients. Ikink et al.[25] and Ruhnke et al.[26] used IV paracetamol and NSAID's. Oral diazepam drops were administered to the patients in the Ruhnke et al.[26] study, when they requested it. Vaessen et al.[27] studied the sedation technique for HIFU therapy. This was the only identified anaesthetic related HIFU study. Conscious sedation with multimodal analgesia was administered (which was comparable to what was administered in this CHBAH study), consisting of oral oxycodone 5mg, 1g IV paracetamol, 75mg IV diclofenac and an infusion of propofol/ketamine (mean dose 1309mg/39.5mg, respectively). Although the timing of when these drugs were administered differ from this CHBAH study.

In this study intraoperative analgesic requirements, in HIFU therapy, were influenced by multiple fibroids, treatment time, energy used and BMI. Patients, in this study, with multiple fibroids had longer treatment and sonification times, higher energy used (although not statistically significant) and were likely to require higher

dosages of short-acting opioids (p=0.002). Although patients in studies done by Barnard et al.[23] and Ikink et al.[25] also had a predominance of multiple fibroids, less intraoperative analgesia was used in these studies. Patients with an increased treatment time, in this study, had a high likelihood of requiring higher doses of short- (p=0.004) and long-acting opioids. Barnard et al.,[23] Jacoby et al.[24] and Ruhnke et al.[26] recorded longer treatment times than in this study but required less intraoperative analgesia. In this study, an increase in energy used had a high likelihood of increasing long-acting opioid requirements (p=0.002). Although higher energy was used in both studies done by Cheng et al.[20] and Wang et al.,[22] less intraoperative analgesia was administered to these patients. Patients who had a normal BMI in this study, were likely to require less intraoperative analgesia, while those who were overweight and obese had a higher likelihood of requiring higher doses of short- and long-acting opioids. Though the studies by Cheng et al.,[20] Chen et al.,[21] Wang et al.[22] and Ikink et al.[25] did not record BMI's, the studies by Barnard et al.,[23] Jacoby et al.,[24] Ruhnke et al.[26] and Vaessen et al.[27] did. The BMI of these patients was very similar to that of this study and yet again less intraoperative analgesia was administered to these patients.

Multiple fibroids, treatment time, energy used and BMI in the studies discussed did not result in a need for as much intraoperative analgesia as in this study. Sadhasivam et al.[28] stated: "Pain is a highly complex, predominantly subjective, dynamic phenomenon that involves biological, psychological and social factors… and it is influenced by race". One possible explanation is that this study is comprised of a homogenous group of patients which were 98.7% black, there might be a cultural predisposition to a decreased pain threshold. Also, the possibility of chronic pelvic pain, due to delayed presentation for HIFU therapy, ought to be explored. A study published by Barnard et al,[23] published in May 2018 concluded that woman with higher baseline VAS scores, presenting for HIFU therapy, were more likely to require opioid medication to control postoperative pain (p=0.001). This might also be true for intraoperative analgesic requirements.

This study was limited in that it was a retrospective study that did not quantify pain. A recommendation for future research is a prospective study on pain in the preoperative, intraoperative and postoperative period, using a validated pain score.

**Conclusion**

Most of the patients presenting for HIFU therapy at CHBAH have multiple fibroids and judging by the intraoperative analgesia administered, HIFU treatment appears to be very painful, which is not in keeping with most other studies.

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## Section 4: Appendices

### 4.1 Ethics clearance

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R14/49 Dr A Ferreira

**HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)**
**CLEARANCE CERTIFICATE NO. M171011**

| | |
|---|---|
| **NAME: (Principal Investigator)** | Dr A Ferreira |
| **DEPARTMENT:** | School of Clinical Medicine<br>Department of Anaesthesiology<br>Chris Hani Baragwanath Academic Hospital |
| **PROJECT TITLE:** | Uterine fibroid characteristics and intraoperative analgaesic requirements during high intensity frequency ultrasound in a central hospital |
| **DATE CONSIDERED:** | 27/10/2017 |
| **DECISION:** | Approved unconditionally |
| **CONDITIONS:** | |
| **SUPERVISOR:** | Professor J Scribante |
| **APPROVED BY:** | Professor CB Penny, Chairperson, HREC (Medical) |
| **DATE OF APPROVAL:** | 20/04/2018 |

**This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.**

**DECLARATION OF INVESTIGATORS**

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on 3rd floor, Phillip V Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.
I/We fully understand the conditions under which I am/we are authorised to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to resubmit to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in **October** and will therefore be due in the month of **October** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

23/04/2018.
Date

**PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES**

## 4.2 Post graduate committee approval

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Private Bag 3 Wits, 2050
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Reference: Mrs Sandra Benn
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13 December 2017
Person No: 1578637
PAG

Dr A Ferreira
70A Kasteelstraat
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Dear Dr Ferreira

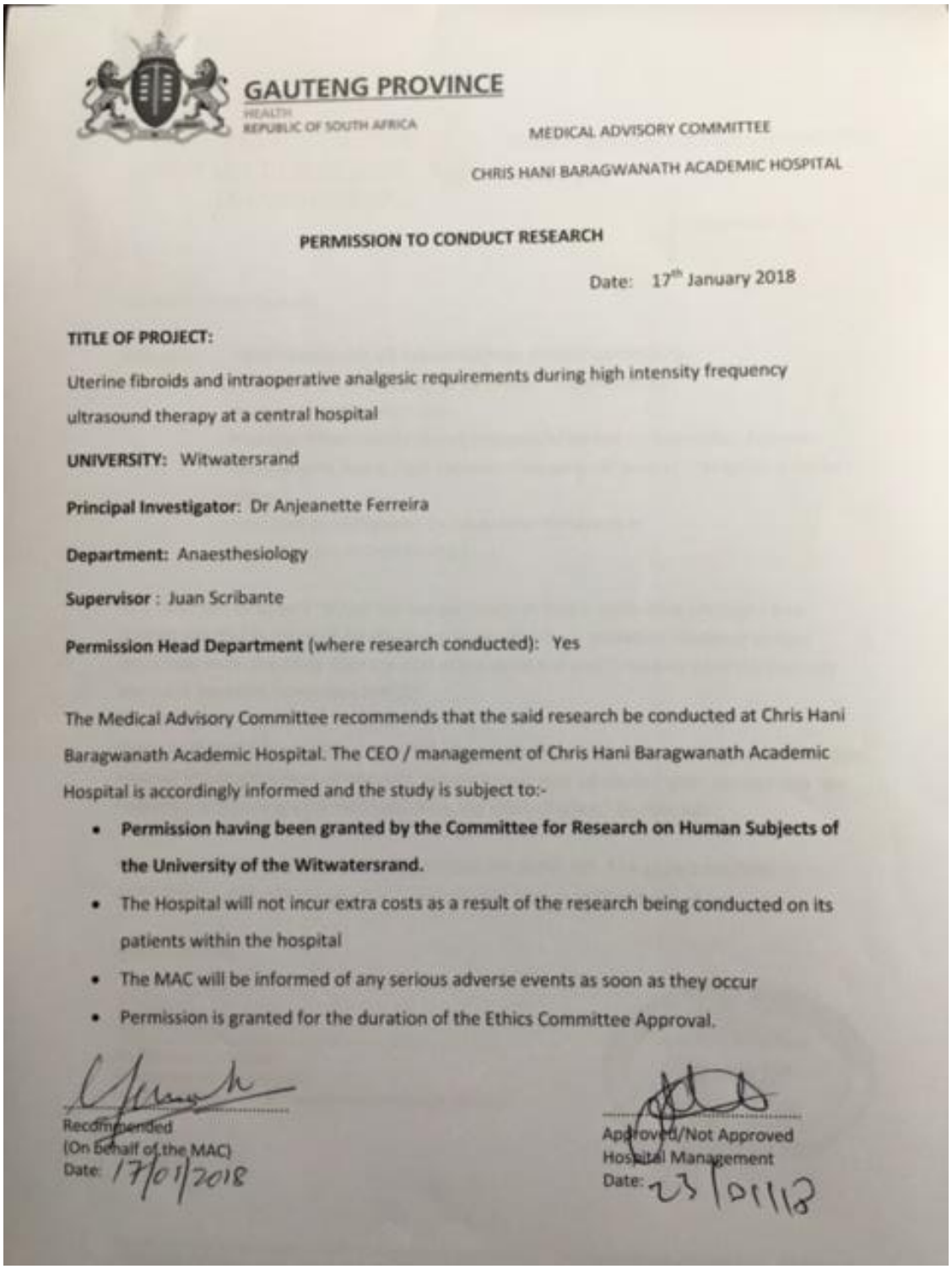
**Master of Medicine: Approval of Title**

We have pleasure in advising that your proposal entitled *Uterine fibroid characteristics and intraoperative analgesic requirements during high intensity frequency ultrasound therapy at a tertiary hospital* has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

## 4.3 Approval from the Chief Executive Officer CHBAH



GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

MEDICAL ADVISORY COMMITTEE

CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

**PERMISSION TO CONDUCT RESEARCH**

Date: 17th January 2018

**TITLE OF PROJECT:**

Uterine fibroids and intraoperative analgesic requirements during high intensity frequency ultrasound therapy at a central hospital

**UNIVERSITY:** Witwatersrand

**Principal Investigator**: Dr Anjeanette Ferreira

**Department:** Anaesthesiology

**Supervisor** : Juan Scribante

**Permission Head Department** (where research conducted): Yes

The Medical Advisory Committee recommends that the said research be conducted at Chris Hani Baragwanath Academic Hospital. The CEO / management of Chris Hani Baragwanath Academic Hospital is accordingly informed and the study is subject to:-

- **Permission having been granted by the Committee for Research on Human Subjects of the University of the Witwatersrand.**
- The Hospital will not incur extra costs as a result of the research being conducted on its patients within the hospital
- The MAC will be informed of any serious adverse events as soon as they occur
- Permission is granted for the duration of the Ethics Committee Approval.

Recommended
(On behalf of the MAC)
Date: 17/01/2018

Approved/Not Approved
Hospital Management
Date: 23/01/18

**Section 5: Annexure**

# Uterine fibroid characteristics and intraoperative analgesic requirements during high intensity focused ultrasound therapy at a central hospital

**Anjeanette Ferreira**

**1578637**

| | |
|---|---|
| **Supervisor** | Juan Scribante<br>Department of Anaesthesiology |
| **Co-supervisor** | Helen Pierre<br>Department of Anaesthesiology |
| **Co-supervisor** | Johan Kotze<br>Department of Anaesthesiology |

## 1. Introduction

Uterine fibroids are benign smooth muscle neoplasms of the uterus that affect 25% – 44 % of women in the reproductive age group and occur in over 70% of women by the onset of menopause (1,2). They can either be asymptomatic (in up to 50% of cases) or they can present with acute or chronic symptoms such as excessive uterine bleeding, abdominal pain, recurrent urinary tract infections and/or problems with fertility (3).

Treatment of symptomatic uterine fibroids can be accomplished by taking pharmacological agents, undergoing surgery or by radiological intervention. Treatment depends on the patient's age, health, fibroid size, severity of symptoms and the need to maintain fertility or not (4–8). Pharmacological agents do not remove the fibroid but do improve the symptom profile and the patient's quality of life. Side effects of these agents and regrowth of the uterine fibroid usually limit their use, and they are therefore used as a temporary treatment measure. They reduce the size of the fibroid(s), and minimise the risk of bleeding when used as an adjuvant to surgery (9).

Hysterectomy used to be the most common treatment for uterine fibroids (10), but due to prolonged hospitalisation, postoperative complications and loss of the uterus (11), an increasing demand for less invasive resolving techniques developed. Less invasive laparoscopic techniques (such as laparoscopic myomectomy, uterine artery embolization (UAE), thermo-ablative treatments) (12), together with high intensity focused ultrasound (HIFU), a non-invasive technique, are becoming increasingly popular. These strategies allow for conservation of the uterus and have many advantages over open surgical procedures including: lower morbidity, faster recovery and shorter hospital stay. It permits the use of sedation rather than a general anaesthesia (5,13,14).

Energy carried in ultrasound waves has the ability to interact with human tissue. This has been recognised for many years, as early as the year 1927. The therapeutic use was recognised because of "the ability of ultrasound energy to cause a rise in tissue

temperature that can lead to cell death".(3). HIFU uses the physical effect of ultrasound on tissues. It raises and maintains the temperature of an isolated part of the tissue to above 60 °C for a second or longer, which causes coagulative necrosis and immediate cell death (15).

The HIFU unit at CHBAH (for uterine fibroid therapy) was the first to operate in Africa. The aim of HIFU therapy is to reduce or eliminate the symptoms caused by uterine fibroids (16). The patient is positioned prone with the acoustic pathway passing from the transducer through a water reservoir on which the patient is positioned (3). The water reservoir is devoid of air bubbles to prevent deflection of ultrasound waves off them. The water is used as a medium for ultrasound waves to travel through. Patients going for HIFU treatment will have their skin (overlying the area of treatment) submerged in the water. Alternatively, a coupling medium (water-filled cushion or gel pad) is used between a sealed water reservoir and the skin over the treatment area (16).

The system plots the individual sonifications and shows the pathway that each sonication will require. This is achieved by the transducer which can be tilted in all directions by up to ± 20° to find a suitable pathway. All these pathways are carefully examined to ensure that no beams pass through any structures that ought to be avoided, e.g. the small bowel. The distance of the beam passing through the fibroid is checked as large neurovascular bundles lie behind the uterine fibroid. The neurovascular bundles are at risk of injury as some energy deposition can remain after the beam has passed through the fibroid, and this will present intraoperatively as a sharp pain radiating down the leg (17).

Once correct positioning has been achieved, the target volume defined, and the treatment planned, verification sonifications are performed. Once the operators are satisfied that the targeting is accurate, they may proceed with the treatment cycle (3). High intensity ultrasonic thermal impulses are repeatedly directed until the entire volume of the fibroid is treated.

The protocol used for HIFU therapy at CHBAH was compiled and updated in September 2016. All the patients are admitted to the ward the day before the

procedure. A standard preoperative assessment is done and the normal nil per os guidelines are followed.

Patients are counselled extensively about the need to lie still during HIFU therapy and about the role of the emergency button. This button is handed to them in theatre and it is provided as a means for them to communicate any discomfort or pain experienced during HIFU therapy. The push of the button halts any further treatment. This is to minimise the risk of neurovascular bundle injury.

Patients undergoing HIFU therapy can return to their normal daily activities within a day (13), compared to about 10 days usually needed after uterine artery embolisation or six weeks after myomectomy or hysterectomy (13,14). This non-invasive technique results in symptomatic relief for more than two years and only 10 ─ 15% of patients require further treatments (18).

Although HIFU therapy for uterine fibroids has been available since 1992 (19), literature available on pain management and anaesthesia in HIFU therapy for uterine fibroids is limited. Pain management varies for uterine HIFU therapy. Many treatment centres make use of conscious sedation intravenously using a short-acting benzodiazepine (midazolam 1 ─ 4 mg) combined with fentanyl (50 ─ 400 mcg) (5,6,20–23). NSAID's (diclofenac 25 ─ 75 mg intramuscular) or ibuprofen 400 mg orally) were added to fentanyl and midazolam in one study (24). This is compared to using only a premedication (drugs) in other studies (18,25). Two identified studies have completed HIFU therapy in compliant patients, without giving any premedication, analgesia or sedation (26,27).

## 2. Problem statement

Although HIFU therapy has been used to treat uterine fibroids for more than two decades (19), there is limited literature available on pain and anaesthesia management for patients undergoing this therapy. Many treatment centers make use of conscious sedation with intraoperative analgesia as their anaesthetic technique.

Minimal sedation and analgesia is provided and patients appear to tolerate the procedure well (6,7,21,23,28,29).

In the literature, several studies used a single dimensional pain scale to rate the intensity of pain during uterine fibroid HIFU therapy (3,6,21,24,29–31). Five studies (6,21,24,29,30) had similar results using the visual analogue pain score. In none of these studies was a score of more than 5 (out of 10) reported at any given point during HIFU therapy.

In contrast to the pain experienced during HIFU therapy in previous studies, the clinical impression at CHBAH is that HIFU therapy for uterine fibroids is very painful. It is possible that the demographics of our population and the uterine fibroid characteristics treated at CHBAH can explain this difference.
Studies describing the uterine fibroid characteristics and the intraoperative analgesic requirements during HIFU therapy, in the South African population, have not been identified nor is this information available for the patient population at CHBAH.

## 3. Aim

The aim of the study is to describe the uterine fibroid characteristics and the intraoperative analgesic requirements of patients undergoing HIFU therapy at CHBAH.

## 4. Objectives

The primary objectives of the study are to:

- describe the demographics of the patients presenting for uterine fibroid HIFU therapy
- describe the characteristics of the uterine fibroids
- describe HIFU therapy for uterine fibroids
- describe intraoperative analgesic requirements
- determine factors associated with intraoperative analgesic requirements.

## 5. Research assumptions

The following definitions will be used in the study.

**Characteristics of uterine fibroids**: will describe the number of fibroids (single/multiple), the location, type and the size of the fibroids.

**HIFU therapy:** describes the treatment time, sonification time and the watts used.
**Treatment time:** is the time from when the patient was put on the theatre table to the time when the HIFU therapy is completed
**Sonification time:** the total time of high focused ultrasound waves emitted, targeting the uterine fibroids.

**Pain assessment:** No pain assessment scale is used. Total intraoperative analgesic requirements will be used as an indication of pain.
Intraoperative analgesia is given to the patient

- pre-emptively according to the protocol
- when the patient pushes the emergency-call button in response to pain experienced
- when indicated through clinical interpretation of vital signs, such as an increased heart rate, blood pressure and/or respiratory rate.

**Records:** will include the HIFU unit record as well as the anaesthetic record.

## 6. Demarcation of study field

The study will be conducted at CHBAH which is a 2888 bed central hospital. HIFU therapy has a dedicated operating theatre. Approximately 260 HIFU cases are done annually, with an average of 5 cases per week. The HIFU unit in CHBAH opened in October 2015.

## 7. Ethical considerations

Approval to conduct the study will be obtained from the Human Research Ethics Committee (Medical) and the Graduate Studies Committee of the University of the Witwatersrand. Approval will be obtained from the Medical Advisory Committee of CHBAH (Appendix 1). Approval to access stored records will be obtained from the record gatekeepers at the HIFU unit (Appendix 2) and the Department of Anaesthesiology (Appendix 3).

Being a retrospective study, no patient consent is needed. Patient details will be kept confidential. A list with patient names, hospital numbers and study numbers will be kept separately. Only the researcher and supervisors will have access to the raw data.

First, the data will be collected from the records of patients who have undergone HIFU therapy. The patient name and hospital number will be matched to the patient's anaesthetic record which is safely stored in the Department of Anaesthesiology in CHBAH. The intraoperative analgesic requirements will be collected from the anaesthetic record and the opioid range (mcg/kg and mg/kg) will be calculated for both short-acting and long-acting opioids. Data will be stored securely on a password-protected, electronic spreadsheet for six years after completion of the study. The study will be conducted according to the principles of the Declaration of Helsinki (32) and the South African Guidelines for Good Clinical Practice (33).

## 8. Data collection

### a. Research design

A retrospective, contextual, descriptive research design will be followed in this study.

This study is retrospective, as it will "measure variables that have occurred in the past" (34). The records of the patients are collected after the HIFU therapy has taken place.

A contextual study is one which refers to a specific group or population, defined by De Vos et al. (35) as a “small-scale world”. This study is contextual in that it will be conducted at CHBAH.

A descriptive study is intended to describe variables, the researcher defines the sample and does not manipulate any variables (34). This study will describe the demographic factors, uterine fibroid characteristics, HIFU therapy and intraoperative analgesic requirements of all patients undergoing such HIFU therapy.

**b. Study population**

Records of all patients who have undergone HIFU therapy for uterine fibroids at CHBAH, will be utilised.

**c. Study sample**

**8.3.1 Sample method**

All available patient records will be included in this study.

**8.3.2 Sample size**

The sample size will consist of records of patients who have undergone HIFU therapy for uterine fibroids at CHBAH, dating between 13 October 2015 to 30 September 2017 (including both dates). This will be approximately 350 cases.

**8.3.3 Inclusion and exclusion criteria**

Inclusion criterion in this study is all the records of patients who have undergone HIFU therapy at CHBAH between 13 October 2015 and 30 September 2017.

Exclusion criteria includes:

- missing records
- illegible anaesthetic records.

## 8.4 Data collection

### 8.4.1 Data collection sheet

The data collection sheet was drafted after reviewing the literature, thereby ensuring content validity. It was reviewed by the head of the HIFU unit as well as a senior anaesthetist with experience in HIFU sedation thereby ensuring content and face validity. Data will be collected according to the data collection sheet (Appendix 4).

It will include the following information:

- patient demographics
- uterine fibroid characteristics
- HIFU therapy
- intraoperative analgesic requirements.

### 8.4.2 Data collection process

Once the relevant approvals have been received, data will be collected from the HIFU records in the HIFU unit at CHBAH as well as the anaesthetic records from the Department of Anaesthesiology.

Data that has been entered on the HIFU records in the unit will provide information on the patient demographic factors, uterine fibroid characteristics and HIFU therapy factors. The intraoperative analgesic requirements will be taken from the anaesthetic record and the opioid ranges will be calculated.

The anaesthetic record is a pre-printed record, which is completed manually by the anaesthetist giving the anaesthetic. It is a record that has a duplicate page at the back. After completion of the HIFU therapy, at the time of discharge from the HIFU

unit, the duplicate page of the anaesthetic record is placed in the patient's file. The original copy of the anaesthetic record is collected and securely stored in the Department of Anaesthesiology.

Patient records will be assigned a study number. The study number will be recorded together with the patient's name and hospital number on a separate Microsoft Excel™ spreadsheet. This document will be password protected and will allow record identification if necessary.

Data capturing will be done by one researcher. The records will not be removed from the hospital premises.

### 8.5 Data analysis

Data will be analysed in consultation with a biostatistician using STATA® version 14.1. Descriptive and inferential statistics will be used. Categorical variables will be analysed using frequencies and percentages. Numerical variables will be analysed using means and standard deviations or medians and interquartile ranges depending on the distribution of the data.

Correlations will be done between both short-acting and long-acting opioid ranges given intraoperatively and

- time of sonification
- total volume of fibroid treated
- BMI of patient.

If the data is normally distributed a Pearson's product-moment correlation will be used and, if not, a Spearman's rank-order correlation will be done.

A logistic regression model will be used, adjusting the effect of each variable on the intraoperative analgesic requirement. A p-value of $<0.05$ will be considered as statistically significant.

## 9. Significance of the study

HIFU therapy for uterine fibroids is becoming increasingly popular having many advantages over open surgical procedures including: lower morbidity, faster recovery and shorter hospital stay. It permits for the use of sedation rather than a general anaesthesia (5,13,14).

A study done in 2007, in a public hospital in South Africa, described that fibroid related menorrhagia was the most common indication for hysterectomy (23%), followed by abnormal uterine bleeding (14.9%. The author further states that in 53.3% of black African women, fibroids were the causative condition of their presenting complaint (36). A study by Marshall et al (2) found that fibroids are more prevalent, present at an earlier age, and are more commonly the reason for hysterectomy in black woman, when compared with the general population (2).

This study will describe the demographics of woman receiving HIFU therapy for uterine fibroids at CHBAH. The uterine fibroid characteristics will be described, together with the HIFU therapy and intraoperative analgesic requirements. Although HIFU therapy for uterine fibroids has been used for more than two decades, it was only introduced at CHBAH two years ago. An improved knowledge of the effect of different variables on intraoperative analgesic requirement may influence analgesic management.

## 10. Validity and reliability of the study

According to Botma et al (37), validity represents " the degree to which measurements represent the true value" and the reliability represents " the consistency of the measure achieved" (36).

Validity and reliability of this study will be maintained by:

- using the appropriate research design
- using a retrospective design, thus preventing anesthetists from changing their practice in response to participating in a study

- content validity of the data collection sheet was ensured by reviewing the available literature
- face and content validity of data collection sheets was ensured by incorporating suggestions from the head of the HIFU unit at CHBAH and a senior anaethetist with HIFU sedation experience
- completing a standardised data collection sheet for every patient
- checking every tenth data entry point to ensure accuracy
- analyzing data in consultation with a biostatistician.

## 11. Potential limitations of the study

Limitations are those restrictions or problems that reduce the assumptions that can be made from the findings of a study (34).

The study will be contextually done at CHBAH. The results therefore may not be generalised to include other HIFU units in hospitals elsewhere.

Using a retrospective study design, the reliance upon completed records for data analysis as well as the absence of intraoperative pain scores, are both potential limitations.

## 12. Project outline

| **Activity** | Aug 2017 | Sept 2017 | Nov 2017 | Jan 2018 | Feb 2018 | Mar 2018 | April 2018 | Jun 2018 | Jul 2018 |
|---|---|---|---|---|---|---|---|---|---|
| Proposal preparation | | | | | | | | | |
| Literature review | | | | | | | | | |
| Proposal Submission | | | | | | | | | |
| Ethics Approval | | | | | | | | | |
| Postgrad Approval | | | | | | | | | |
| Data collection | | | | | | | | | |
| Data analysis | | | | | | | | | |
| Article preparation | | | | | | | | | |
| Submission | | | | | | | | | |

## 13. Financial plan

| Item | Number | Cost | Total |
|---|---|---|---|
| Printing | 1600 | R1/page | R1600 |
| Binding | 4 | R200 | R 800 |
| Total | | | R2400 |

The Department of Anaesthesiology will cover the cost of printing and paper for the proposal, ethics and postgraduate approvals.

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## Appendix 1: Request to the Medical Advisory Committee of Chris Hani Baragwanath Academic Hospital

Dr Anjeanette Ferreira
Department of Anaesthesiology
University of the Witwatersrand

Attention: The Medical Advisory Committee of Chris Hani Baragwanath Academic Hospital

**Re: Uterine fibroid characteristics and intraoperative analgesic requirements during high intensity focused ultrasound therapy at a tertiary hospital**

The Chairperson

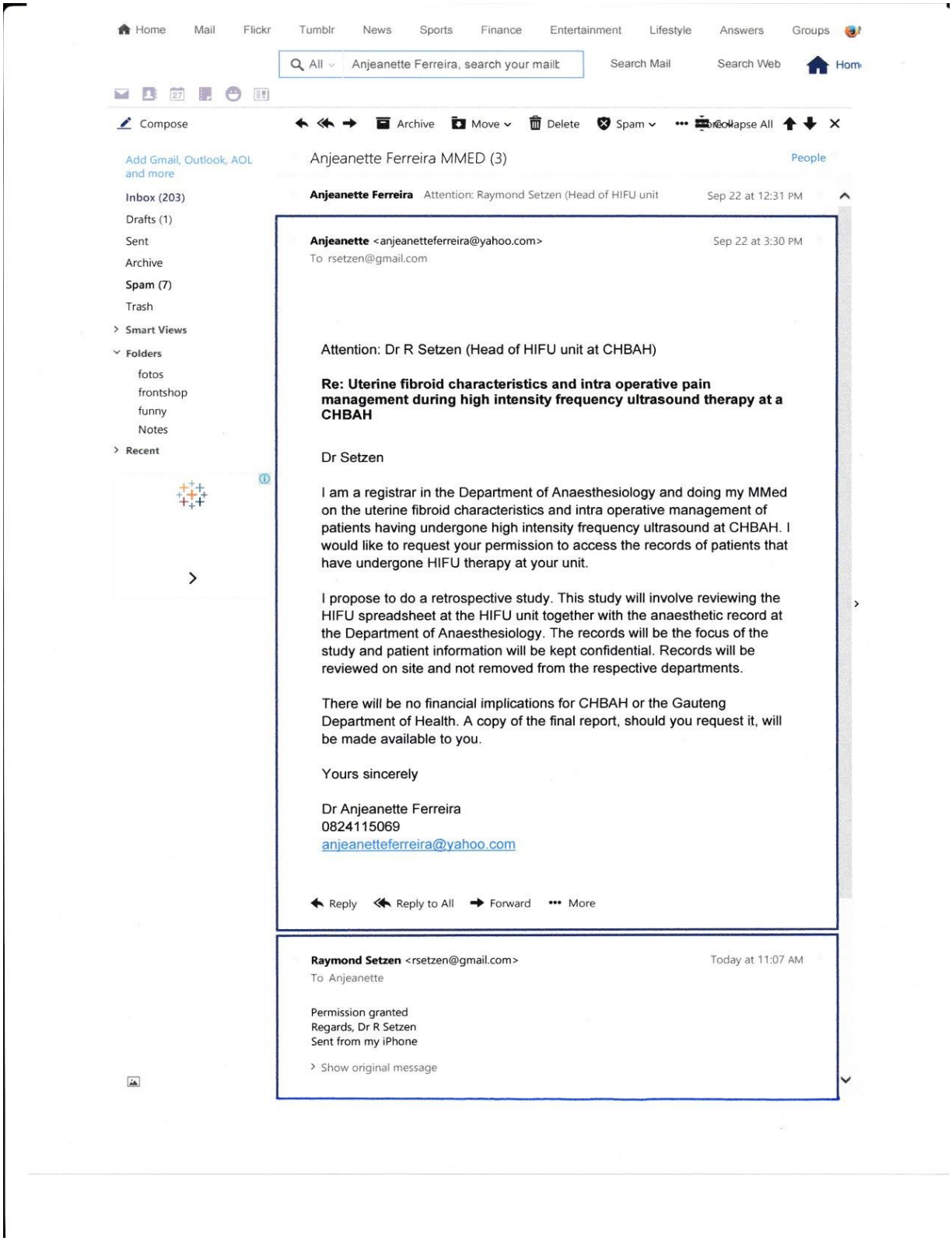
I am a registrar in the Department of Anaesthesiology. I propose to do a retrospective analysis of the uterine fibroid characteristics and intraoperative management of patients having undergone high intensity focused ultrasound at CHBAH. The study has been approved by the Human Research Ethics Committee (Medical) (number XXX) and Graduate Studies Committee.

This audit will involve reviewing the high intensity focused ultrasound (HIFU) spreadsheet at the HIFU unit together with the anaesthetic record in the Department of Anaesthesiology. The records will be the focus of the study and patient information will be kept confidential. Records will be reviewed where they are stored and will not be removed from the premises.

There will be no financial implications for CHBAH or the Gauteng Department of Health. A copy of the final report, should you request it, will be made available to you.
Yours sincerely

Dr Anjeanette Ferreira
0824115069
anjeanetteferreira@yahoo.com

## Appendix 2: Permission from the Head of Clinical Unit and gatekeeper of the HIFU unit at CHBAH



Home Mail Flickr Tumblr News Sports Finance Entertainment Lifestyle Answers Groups

All Anjeanette Ferreira, search your mail Search Mail Search Web Hom

Compose Archive Move Delete Spam Collapse All

Add Gmail, Outlook, AOL and more

Inbox (203)
Drafts (1)
Sent
Archive
Spam (7)
Trash
Smart Views
Folders
fotos
frontshop
funny
Notes
Recent

Anjeanette Ferreira MMED (3) People

**Anjeanette Ferreira** Attention: Raymond Setzen (Head of HIFU unit Sep 22 at 12:31 PM

**Anjeanette** <anjeanetteferreira@yahoo.com> Sep 22 at 3:30 PM
To rsetzen@gmail.com

Attention: Dr R Setzen (Head of HIFU unit at CHBAH)

**Re: Uterine fibroid characteristics and intra operative pain management during high intensity frequency ultrasound therapy at a CHBAH**

Dr Setzen

I am a registrar in the Department of Anaesthesiology and doing my MMed on the uterine fibroid characteristics and intra operative management of patients having undergone high intensity frequency ultrasound at CHBAH. I would like to request your permission to access the records of patients that have undergone HIFU therapy at your unit.

I propose to do a retrospective study. This study will involve reviewing the HIFU spreadsheet at the HIFU unit together with the anaesthetic record at the Department of Anaesthesiology. The records will be the focus of the study and patient information will be kept confidential. Records will be reviewed on site and not removed from the respective departments.

There will be no financial implications for CHBAH or the Gauteng Department of Health. A copy of the final report, should you request it, will be made available to you.

Yours sincerely

Dr Anjeanette Ferreira
0824115069
anjeanetteferreira@yahoo.com

Reply Reply to All Forward More

**Raymond Setzen** <rsetzen@gmail.com> Today at 11:07 AM
To Anjeanette

Permission granted
Regards, Dr R Setzen
Sent from my iPhone

Show original message

**Appendix 3: Permission from the Head of Clinical Unit and gatekeeper of the Department of Anaesthesiology at CHBAH**

Attention: Prof Lundgren (Head of the Department of Anaesthesiology at CHBAH)

Re: Uterine fibroid characteristics and intraoperative analgesic requirement during high intensity focused ultrasound therapy at a CHBAH

Prof Lundgren

I am a registrar in the Department of Anaesthesiology and doing my MMed on the uterine fibroid characteristics and intraoperative management of patients having undergone high intensity focused ultrasound at CHBAH. I would like to request your permission to access the anaesthetic records of patients that have undergone HIFU therapy.

I propose to do a retrospective study. This study will involve reviewing the HIFU spreadsheet at the HIFU unit together with the anaesthetic record at the Department of Anaesthesiology. The records will be the focus of the study and patient information will be kept confidential. Records will be reviewed on site and not removed from the respective departments.

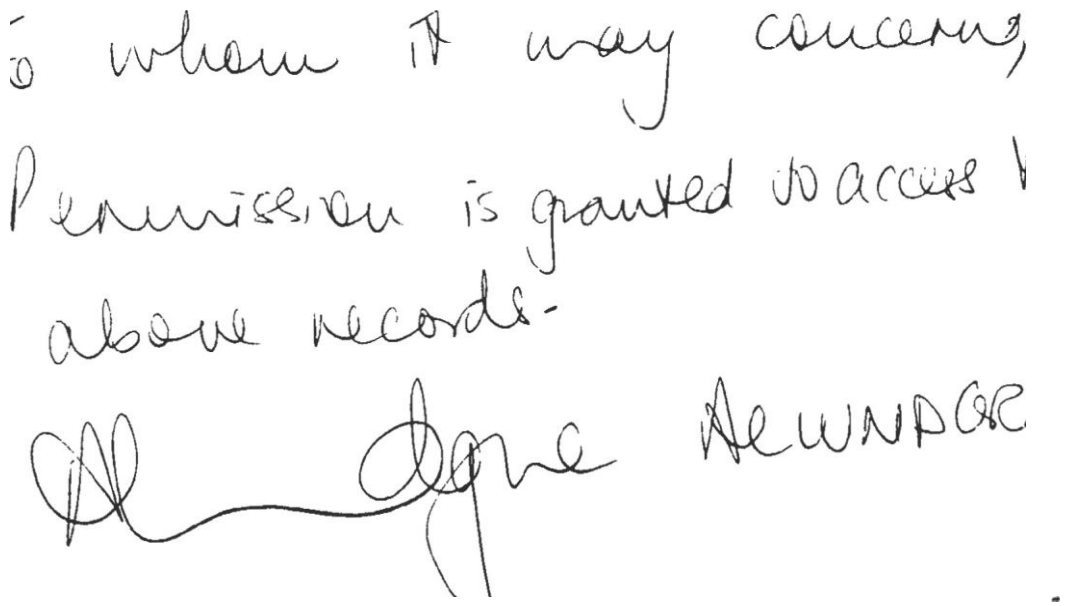
There will be no financial implications for CHBAH or the Gauteng Department of Health. A copy of the final report, should you request it, will be made available to you.

Yours sincerely

Dr Anjeanette Ferreira

0824115069

anjeanetteferreira@yahoo.com



**Appendix 4: Data collection sheet**

| | Patient 1 | Patient 2 | Patient 3 | Patient 4 | Patient 5 |
|---|---|---|---|---|---|
| **Demographic Factors** | | | | | |
| Age (years) | | | | | |
| Weight (kg) | | | | | |
| Height (m) | | | | | |
| BMI ($kg.m^2$) | | | | | |
| Parity | | | | | |
| Gravity | | | | | |
| Race | | | | | |
| **Uterine fibroid characteristics** | | | | | |
| Single (S) or Multiple (M) | | | | | |
| Type of fibroid<br>Mucosal (M)<br>Intramural (IM)<br>Submucosal (SM)<br>Subserosal (SS) | | | | | |
| Location of fibroid<br>Anterior wall (A)<br>Posterior wall (P)<br>Lateral wall (L)<br>Fundus (F) | | | | | |
| Fibroid volume ($cm^3$) | | | | | |
| **HIFU therapy factors** | | | | | |
| Treatment time (min) | | | | | |
| Sonification time (min) | | | | | |
| Power (W) | | | | | |
| **Intraoperative sedation (total dosages)** | | | | | |
| Midazolam (mg) | | | | | |
| Propofol (mg) | | | | | |
| Dexmedetomidine (mg) | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| **Intraoperative total analgesia dosages** | | | | | |
| IV paracetamol (g) | | | | | |
| NSAIDS (mg) | | | | | |
| Dexamethasone (mg) | | | | | |
| Short-acting opioids<br>Fentanyl (ug)<br>Sufentanil (ug)<br>Alfentanil (ug) | | | | | |
| Opioid ranges<br>Fentanyl (ug/kg)<br>Sufentanil (ug/kg)<br>Alfentanil (ug/kg) | | | | | |
| Long-acting opioids<br>Morphine (mg)<br>Pethidine (mg) | | | | | |
| Long-acting opioid ranges<br>Morphine (mg/kg) | | | | | |
| Ketamine (mg) | | | | | |