



The efficacy of intra-arterial lignocaine as an adjuvant analgesic in the management of pain following uterine artery embolisation – a comparative study of outcomes.

Submitted by: Dr Gercois Paul Human

Student Number: HMNGER001

Supervisor: Dr Gary Sudwarts

Co-Supervisor: Dr Maja Julia Wojno

A research report submitted to the

Faculty of Health Sciences, University of Cape Town,

in partial fulfilment of the requirements for the degree of

Master of Medicine in Diagnostic Radiology

October 2021

The copyright of this thesis vests in the author. No quotation from it or information derived from it is to be published without full acknowledgement of the source. The thesis is to be used for private study or non-commercial research purposes only.

Published by the University of Cape Town (UCT) in terms of the non-exclusive license granted to UCT by the author.

DECLARATION

I, Gercois Paul Human hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

I empower the university to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

Signature:

Date: 29 May 2021

Table of Contents

List of figures:.....	4
Abbreviations:.....	4
Abstract:.....	5
Chapter 1 – Literature review	6
Introduction	6
Background	6
Epidemiology.....	6
Pathology and Pathogenesis	7
Presentation.....	7
Management.....	7
Uterine artery embolisation Procedure.....	8
Uterine artery embolisation: Complications.....	9
References	12
Chapter 2 – Full Text Journal Article for Submission	14
Title	14
Abstract:.....	14
Introduction	15
Methods and Material:	15
Procedure:.....	16
Statistical Analysis.....	17
Results:.....	18
Discussion:	22
Study Limitations:	23
Conclusion:.....	24
Acknowledgements:.....	24
Competing Interest:	24
Author’s contribution:	24
References:	25

List of figures:

Figure 1 - Symptoms of Uterine Fibroids	18
Figure 2 - Post procedural Pain	19
Figure 3 - Post procedural Nausea	20
Figure 4 - Post procedural Constipation	21

Abbreviations:

ANOVA: Analysis of Variance

PES: Post Embolisation Syndrome

UAE: Uterine Artery Embolisation

VAS: Visual Analogue Scale

Abstract:

Background:

Uterine artery embolisation (UAE) for symptomatic fibroids has been shown to be an effective and beneficial procedure in our South African population, especially considering any cultural stigma related to hysterectomy. Post procedural pain following UAE can be very significant. Regular review of pain management protocols in our population is therefore warranted. In particular, the benefit of intra-arterial lignocaine as an adjunctive analgesic following UAE remains uncertain.

Method:

A single institution retrospective comparative study was undertaken through review of folders of patients who were treated for symptomatic uterine fibroids by UAE between July 2016 and November 2019. Two groups were compared – those who underwent UAE without the use of intra-arterial lignocaine (Control group) and those who received intra-arterial lignocaine (Study group). Baseline characteristics and periprocedural outcomes were compared together with an 11-Point pain scale which was recorded during the post procedural rounds at the end of the day.

Results:

A total of 473 patients were included in the study, with 142 patients in the Control group and 331 patients in the study group. No significant differences were found in the 11-point pain scores between the two groups ($p=0.34$). However, additional medication usage was slightly higher in the Control group ($p=0.05$), together with longer hospital stay ($p<0.01$). Patients from the Study group also reported less nausea on the day of the procedure ($p<0.01$) and felt markedly less constipated on day 2 ($p<0.01$).

Conclusion:

Despite no significant overall pain score reduction, intra-arterial lignocaine after UAE for uterine fibroids correlated with reduced additional medication use, shorter hospital stays and less feeling of nausea and constipation.

Chapter 1 – Literature review

Introduction

Background

Uterine fibroids are the most common benign tumours in women of reproductive age worldwide. These tumours can have a significant impact on the daily life of affected women. Women of African descent have a higher incidence and health burden of uterine fibroids, with more seeking medical treatment.

Historically uterine fibroids have been treated by removal of the uterus, therefore excluding women wishing to retain their uterus for personal or cultural reasons, or desire to have children.

Since its introduction in 1995, uterine artery embolisation (UAE) has proven to be safe and effective in treating symptomatic uterine fibroids, with the added advantage of uterine preservation.

However, post procedural pelvic pain is a common side-effect of UAE, often requiring anaesthetic support and /or large doses of analgesia that can prolong hospital stay and increase time to recovery.

Intra-arterial lignocaine given during other procedure has shown promise as an adjunctive analgesic by decreasing post procedural pain, pain medication and hospital stay. There are conflicting views on the efficacy of intra-arterial lignocaine after UAE, and the value of additional benefits have not been clarified. We therefore set out to determine the efficacy and any additional benefits of intra-arterial lignocaine after UAE.

Epidemiology

Uterine fibroids may develop in up to 70% of women, a third of whom are estimated will develop substantial symptoms. As many as 50% of women over 50 years of age will have developed uterine fibroids. ^{1,2}

Recently, a higher incidence of uterine fibroids was found in women of African descent. As many as 60% of women at the age of 35 years had already developed uterine fibroids, increasing to almost 70% by the age of 50 years. ^{3,4}

In addition, they also have an increase in severity of the disease, more often requiring therapy. ⁵ Bulman et al found that approximately 50% of women of African descent eventually require treatment, compared to 25% of Caucasian women. ^{6,7}

Pathology and Pathogenesis

Uterine fibroids are benign tumours of Müllerian duct origin originating within the uterus. They consist of smooth muscle and fibroid tissue of a disorganised fibrous nature, with abundant disordered monoclonal smooth muscle cells and a surrounding extracellular matrix consisting of collagen, fibronectin, and proteoglycan. ^{1,3,6,8}

Although the pathogenesis is not completely understood there is abundant evidence supporting the belief that the tumour growth is stimulated by the sex hormones (oestrogen and progesterone) which also explains why these tumours are not common during the menarche or why they regress after menopause. ^{3,6,9}

These tumours are classified based on their location within uterine layers as submucosal, intramural or subserosal. Tumours attached to a fibrous stalk projecting either into the uterine cavity or outside the uterine body is classified as pedunculated. ^{1,3,6}

Presentation

Women affected by uterine fibroids are often asymptomatic, but many may suffer from a multitude of symptoms varying clinical impact. Menstrual cycle complaints with excessive menstruation manifesting as prolonged bleeding and/or increased volume of flow, is the most common complaint. Resultant anaemia often requiring blood transfusion is not uncommon. In addition, dysmenorrhoea, severe abdominal pain, pelvic pressure, urinary incontinence or problems of infertility are also frequent. ^{1-3,7,9,10}

Submucosal uterine fibroids have been proposed to disrupt the normal uterine peristaltic movement and contractility which can impede fertilisation. Pregnancy-related problems often present in the form of preterm labour and infertility, with miscarriages twice as common in women suffering from uterine fibroids. ¹

It is postulated that submucosal fibroids increase uterine contractions, leading to preterm labour. These problems not only affect the woman's quality of life, but indirectly are a burden on society and health care services. ⁹

Management

Not all women who develop uterine fibroids will require management. Only symptomatic women suffering from the complications of fibroids may eventually be treated, including women with large fibroids and infertility. A holistic approach to treatment is recommended, considering the patient's age and desire to maintain fertility as well as their access to treatment. ^{6,9}

Therapeutic options range from medical to surgical. Failure of medical treatment necessitate surgical or radiological management. ³

The mainstay of treatment for uterine fibroids has been hysterectomy and it is also the definitive cure. Uterine fibroid-related cases account for up to 70% of hysterectomies performed annually in the USA. Hysterectomy has a 3% incidence of major complications, including mortality. This would be a less favourable option for patients who would still like to fall pregnant. ^{4,9}

Alternatively, patients undergo myomectomy, in which each individual fibroid is removed surgically either by means of open or laparoscopic surgery. Complications associated with myomectomy include adhesion formation, the risk of uterine rupture during pregnancy and fibroid recurrence. Other less invasive options include endometrial ablation, high-intensity focused ultrasound, and UAE. ^{7,9}

Uterine artery embolisation procedure

Uterine artery embolisation is a minimally invasive, percutaneous, image-guided procedure which over the past two decades has proven itself to be a safe and effective treatment option for uterine fibroids, sparing the uterus. It involves the placement of an angiographic catheter into the uterine arteries via a common femoral or radial artery approach. Particulate embolic agents are then injected into the uterine arteries, reducing and occluding uterine blood flow producing an ischemic injury to the fibroids. The fibroids undergo necrosis and shrink over time, while the normal myometrium has enough blood flow from pelvic collateral vessels to recover. ^{2,8,9}

This procedure is often the choice for patients who presenting with symptomatic uterine fibroids who wish to retain their uterus or avoid major surgical intervention for personal or medical reasons.

Prior to the procedure, patients with symptomatic uterine fibroids require a recent gynaecological examination with a Papanicolaou smear and, in certain cases, endometrial sampling to exclude malignancy. ^{7,8}

Pregnancy, untreated gynaecological infection or current gynaecological malignancy are contra-indications to the procedure. ^{6,7,10}

Recent pelvic Magnetic Resonance Imaging is recommended to evaluate the uterine anatomy and to exclude other aetiologies that could contribute to pelvic pain or uterine bleeding.

Imaging further helps to classify uterine fibroids according to their location and also to determine the likelihood of post-UAE per vaginal passage of a fibroid, as occurs in some submucosal fibroids. It also helps establish a baseline to which follow-up imaging could be compared to determine

successful embolisation.¹⁰ Patients undergo standard pre-operative preparation including being kept nil per mouth for 6 hours, having the necessary blood tests to ensure a normal renal function, haemoglobin level, platelet count and normal clotting.

Minimal to moderate conscious sedation using fentanyl and midazolam is normally utilised, although general anaesthesia, or epidural or spinal anaesthesia can be used in some instances.

Entry into the arterial system is gained via standard femoral or radial artery access. Following placement of a 5-Fr or 6-Fr vascular sheath, the uterine arteries are selected with a 4-Fr or 5-Fr catheter or a 3-Fr co-axial microcatheter and guidewires. Polyvinyl alcohol or trisacryl gelatin particles ranging between 300-1000 micrometres are typically used for UAE. This particulate embolic material is slowly injected into the uterine arteries until near stasis is obtained. This reduction and occlusion of uterine blood flow produces an ischemic injury to the fibroids.^{9,10}

Patients are generally observed for 24 hours after the procedure monitoring their vital signs and administering prescribed pain medication for post procedural pain both patient controlled anaesthetic pump and prescribed analgesia. the nursing staff.

Compared to hysterectomy and myomectomy, UAE has been shown to reduce hospital stay and post procedural blood transfusion, as well as leading to a quicker return to normal activities.⁶

Uterine artery embolisation: Complications

UAE can initiate a cascade of post procedural adverse events, which can be divided into acute (within the first 24 hours), sub-acute (from 24 hours up to a month) and chronic (longer than a month).¹¹

The most frequent side-effect and the greatest challenge after the procedure is pelvic pain. This can be immediate and usually lasts for 12 to 24 hours, with nausea often accompanying the pain. Moderate pain follows and will typically dissipate after a week. One study found that a third of women who underwent UAE experience pain “equal or worse than that of labour despite anti-inflammatory drugs and patient-controlled analgesia”.¹²

The pathophysiology of the pain is thought to be due to ischaemia of the fibroid and transient ischaemia of the normal myometrium.^{3,8,12-15}

Another common adverse effect that follows UAE is the Post Embolisation Syndrome (PES), in which the body is thought to mount an immune response, typically following embolisation of a solid organ. PES encompasses fever, pain, malaise, nausea, and low-grade fever lasting from a few days to a week and is usually readily treated by anti-inflammatories and antipyretics. It occurs in up to 30% of

patients. It is commonly seen in patient who undergo bland or chemoembolisation of the haptic artery, or pre-operative embolisation before nephrectomy or splenectomy. It has been found that persistent pain and fever are the commonest reasons for readmission following UAE. ^{3,7,12-15}

It is vital that patient pain is managed early and adequately, preventing patient from experiencing severe pain or developing PES. Inadequate pain management has been shown to prolong hospitalisation, increase visits to the emergency unit and lead to subsequent readmissions. ^{7,15,16}

Various approaches to combatting post-UAE pain include general and local anaesthesia, hypogastric nerve blocks, patient-controlled analgesia, or intravenous and oral medication. All these techniques have disadvantages of prolonging recovery times, extending hospital stay and increase the side-effects of the medication due to the large amounts often required to combat post UAE pain. ^{7,12-16}

There, a need exists for effective, quick, and adequate pain control with minimal side-effect, shortened hospital stay and quicker recovery time. ¹⁶

However, often high doses of analgesia are needed to control pain which could lead to increased side effects, prolonged hospitalisation and prolonged time to recovery. ¹⁵

Lignocaine is an intermediate-acting local anaesthetic with analgesic, anti-hyperalgesic and anti-inflammatory properties. ^{12,17} Intra-arterial lignocaine has been safely and effectively used since the 1970's to counter the pain caused by injection of older iodinated contrast agents during peripheral arteriography, and since the 1990's to control pain during hepatic chemoembolisation. ^{12,18}

Intra-arterial lignocaine administration during these procedures has been proven to reduce peri- and post procedural pain and decrease concomitant narcotic drug dosage. ^{21,22}

This leads to a reduction in analgesic side-effects, quicker recovery times, shortened hospital stays and decreased readmission rates. However, there are conflicting view on the efficacy of intra-arterial lignocaine administration to manage pain after UAE for symptomatic uterine fibroids. ^{13,14,23}

It is recommended that lignocaine be administered following successful UAE as previous studies reported vasospasm of the uterine arteries prior to administration of lignocaine which in itself could lead to unsuccessful embolisation of uterine fibroids. Vasospasm of the arteries are hypothesized to be due to a transient local endothelial effect of the administered lignocaine and appears to be dose related rather than a peripheral or central-nervous system effect. The effects of vasospasm are pronounced in the sensitive uterine arteries due to their inherent physiologically need to contract during pregnancy. ^{12,18}

Conclusion:

Uterine fibroids cause a significant burden of disease in women of childbearing age. There is an above average prevalence of uterine fibroids in women of African descent. Although various treatment modalities exist, wide-ranging morbidity and personal reasons may limit patient options. UAE is a safe and minimally invasive procedure appealing to patients who would like to retain their uterus to complete their families, to avoid cultural stigma, or in patients who are not fit for general anaesthesia.

Post procedural pain and PES are very common side effects following UAE. These may prove detrimental if managed inadequately, leading to extended recovery times, prolonged hospital stays and increased rates of hospital readmission. It is therefore paramount that peri- and procedural pain be managed adequately to limit the dosage of analgesia and the need for more invasive analgesic techniques.

Intra-arterial lignocaine in other procedures has been proven to be both safe and effective in decreasing post procedural pain, as well as restricting analgesic usage and resultant side-effects. Although the use of lignocaine has been shown to be safe, its efficacy in UAE has not yet been proven.

References

1. McWilliams MM, Chennathukuzhi VM. Recent Advances in Uterine Fibroid Etiology. *Semin Reprod Med.* 2017;35(2):181-189. doi:10.1055/s-0037-1599090
2. Spies JB. Current evidence on uterine embolization for fibroids. *Semin Intervent Radiol.* 2013;30(4):340-346. doi:10.1055/s-0033-1359727
3. Khan A, Shehmar M, Gupta J. Uterine fibroids: current perspectives. *Int J Womens Health.* 2014;6:95. doi:10.2147/IJWH.S51083
4. Rischbieter P, Sinclair C, Lawson A, Ahmad S. Uterine artery embolisation as an effective choice for symptomatic fibroids: Five-year outcome. *South African J Radiol.* 2016;20(1):5 pages. doi:10.4102/sajr.v20i1.959
5. Catherino W, Eltoukhi H, Al-Hendy A. Racial and ethnic differences in the pathogenesis and clinical manifestations of uterine leiomyoma. *Semin Reprod Med.* 2013;31(5):370-379. doi:10.1055/s-0033-1348896
6. De La Cruz MSD, Buchanan EM. Uterine Fibroids: Diagnosis and Treatment. *Am Fam Physician.* 2017;95(2):100-107. <https://www.aafp.org/afp/2017/0115/p100.html>.
7. Bulman JC, Ascher SM, Spies JB. Current Concepts in Uterine Fibroid Embolization. *RadioGraphics.* 2012;32(6):1735-1750. doi:10.1148/rg.326125514
8. Prollius A, De Vries C, Loggenberg E, et al. Uterine artery embolization for symptomatic fibroids. *Int J Gynecol Obstet.* 2004;84(3):236-240. doi:10.1016/j.ijgo.2003.09.006
9. Gupta JK, Sinha A, Lumsden MA, Hickey M. Uterine artery embolization for symptomatic uterine fibroids. *Cochrane Database Syst Rev.* 2014;2014(12). doi:10.1002/14651858.CD005073.pub4
10. Keung JJ, Spies JB, Caridi TM. Uterine artery embolization: A review of current concepts. *Best Pract Res Clin Obstet Gynaecol.* 2018;46:66-73. doi:10.1016/j.bpobgyn.2017.09.003
11. Memtsa M, Homer H. Complications Associated with Uterine Artery Embolisation for Fibroids. *Obstet Gynecol Int.* 2012;2012:1-5. doi:10.1155/2012/290542
12. Noel-Lamy M, Tan KT, Simons ME, Sniderman KW, Mironov O, Rajan DK. Intraarterial Lidocaine for Pain Control in Uterine Artery Embolization: A Prospective, Randomized Study. *J Vasc Interv Radiol.* 2017;28(1):16-22. doi:10.1016/j.jvir.2016.10.001
13. Duvnjak S, Andersen PE. Intra-arterial lidocaine administration during uterine fibroid

- embolization to reduce the immediate postoperative pain: a prospective randomized study. *CVIR Endovasc*. 2020;3(1). doi:10.1186/s42155-020-0099-4
14. Katsumori T, Miura H, Yoshikawa T, Seri S, Kotera Y, Asato A. Intra-Arterial Lidocaine Administration for Anesthesia after Uterine Artery Embolization with Trisacryl Gelatin Microspheres for Leiomyoma. *J Vasc Interv Radiol*. 2020;31(1):114-120. doi:10.1016/j.jvir.2019.09.007
 15. Schirf BE, Vogelzang RL, Chrisman HB. Complications of uterine fibroid embolization. *Semin Intervent Radiol*. 2006;23(2):143-149. doi:10.1055/s-2006-941444
 16. Lampmann LE, Lohle PN, Smeets A, et al. Pain management during uterine artery embolization for symptomatic uterine fibroids. *Cardiovasc Intervent Radiol*. 2007;30(4):809-811. doi:10.1007/s00270-007-9069-7
 17. Daykin H. The efficacy and safety of intravenous lidocaine for analgesia in the older adult: a literature review. *Br J Pain*. 2017;11(1):23-31. doi:10.1177/2049463716676205
 18. Keyoung JA, Levy EB, Roth AR, Gomez-Jorge J, Chang TC, Spies JB. Intraarterial Lidocaine for Pain Control after Uterine Artery Embolization for Leiomyomata. *J Vasc Interv Radiol*. 2001;12(9):1065-1069. doi:10.1016/S1051-0443(07)61592-9
 19. Foo I, Macfarlane AJR, Srivastava D, et al. The use of intravenous lidocaine for postoperative pain and recovery: international consensus statement on efficacy and safety. *Anaesthesia*. 2021;76(2):238-250. doi:10.1111/ANA.15270
 20. El-Boghdadly K, Pawa A, Chin KJ. Local anesthetic systemic toxicity: Current perspectives. *Local Reg Anesth*. 2018;11:35-44. doi:10.2147/LRA.S154512
 21. Eipe N, Gupta S, Penning J. Intravenous lidocaine for acute pain: an evidence-based clinical update. *BJA Educ*. 2016;16(9):292-298. doi:10.1093/bjaed/mkw008
 22. Abusedera MA, Arafa UA, Ali EM. Transcatheter administration of buffered Lidocaine for pain relief due to transarterial chemoembolization for HCC. *Egypt J Radiol Nucl Med*. 2014;45(2):403-408. doi:10.1016/j.ejrn.2014.03.005
 23. Liu S, Li W. Intra-arterial lidocaine for pain control after uterine artery embolization: a meta-analysis of randomized controlled trials. *J Matern Neonatal Med*. 2020. doi:10.1080/14767058.2020.1847079

Chapter 2 – Full Text Journal Article for Submission

Title

The efficacy of intra-arterial lignocaine as an adjuvant analgesic in the management of post procedural pain following uterine artery embolisation for symptomatic uterine fibroids – a comparative study of outcomes.

Abstract:

Background:

Uterine artery embolisation (UAE) for symptomatic fibroids has been shown to be an effective and beneficial procedure in our South African population, especially considering any cultural stigma related to hysterectomy. Post procedural pain following UAE can be very significant. Regular review of pain management protocols in our population is therefore warranted. In particular, the benefit of intra-arterial lignocaine as an adjunctive analgesic following UAE remains uncertain.

Method:

A single institution retrospective comparative study was undertaken through review of folders of patients who were treated for symptomatic uterine fibroids by UAE between July 2016 and November 2019. Two groups were compared – those who underwent UAE without the use of intra-arterial lignocaine (Control group) and those who received intra-arterial lignocaine (Study group). Baseline characteristics and periprocedural outcomes were compared together with an 11-Point pain scale which was recorded during the post procedural rounds at the end of the day.

Results:

A total of 473 patients were included in the study, with 142 patients in the Control group and 331 patients in the study group. No significant differences were found in the 11-point pain scores between the two groups ($p=0.34$). However, additional medication usage was slightly higher in the Control group ($p=0.05$), together with longer hospital stay ($p<0.01$). Patients from the Study group also reported less nausea on the day of the procedure ($p<0.01$) and felt markedly less constipated on day 2 ($p<0.01$).

Conclusion:

Despite no significant overall pain score reduction, intra-arterial lignocaine after UAE for uterine fibroids correlated with reduced additional medication use, shorter hospital stays and less feeling of nausea and constipation.

Introduction

Uterine artery embolisation (UAE) is an established uterine sparing procedure in the management of symptomatic uterine fibroids, especially in patients wanting to retain their uterus or cannot have surgery due to comorbidities.¹⁻⁵

Past studies in South Africa have shown UAE to be both effective and beneficial especially in women of African descent in whom fibroids have a higher prevalence and health burden, and where hysterectomy may carry cultural stigma.^{1,2,5}

Post procedural pain control following UAE is the most common complaint and is a significant clinical challenge often leading to prolonged hospital stay and readmission.^{1,6,7}

The ability to optimally control post procedural pain should decrease patient morbidity, hospital stay and costs, as well as expedite recovery.^{6,8}

Alternative pain management techniques including hypogastric nerve block, epidural anaesthesia and intra-arterial lignocaine have been used to reduce high doses of systemic analgesia and narcotic agents.

Intra-arterial lignocaine has been proven to be effective during hepatic chemoembolisation and peripheral angiography, and safe during UAE.^{3,9,10}

It is preferred that administration of lignocaine follow successful UAE as prior studies reported vasospasm of the uterine arteries due to administration of lignocaine. This may lead to unsuccessful embolisation of the uterine arteries and uterine fibroids. It is hypothesized to be due to a transient local endothelial effect and appears to be dose related. The effects which are pronounced in the sensitive uterine arteries due to its inherent physiologically need to contract during pregnancy.^{3,4}

The efficacy of intra-arterial lignocaine following UAE is not yet fully established. We therefore performed a retrospective comparative study in a sub-Saharan African population to determine the efficacy and adjunctive benefits of intra-arterial lignocaine following UAE for symptomatic fibroids.

Methods and Material:

The present retrospective comparative study was undertaken by review of the medical folders of patients who were treated by UAE for symptomatic uterine fibroids by two intervention radiologists. These were performed at one hospital in Johannesburg and one in Cape Town, both belonging to one institution. These patients underwent uterine artery embolisation between July 2016 and November 2019.

All patients were referred by their gynaecologists for UAE as treatment for symptomatic fibroids. Symptoms included menorrhagia, dysmenorrhoea, metrorrhagia, anaemia, pelvic pressure, dyspareunia and/or infertility.

All the patients preferred UAE as their treatment choice. Presence of fibroids were confirmed on MRI.

The practice introduced intra-arterial lignocaine as adjunctive pain medication as part of their embolisation pain management protocol from September 2017. All patients thereafter received adjunctive lignocaine. The patients were thus divided into two groups – the Control group from July 2016 to September 2017 not receiving lignocaine, and the Study group from September 2017 to November 2019 receiving lignocaine.

Procedure:

All patients underwent initial examination by a registered gynaecologist including a physical examination, Papanicolaou smear, as well as a pelvic MRI prior to the procedure.

After local anaesthetic was given at the arterial entry point, a femoral or radial artery puncture was performed under sonographic guidance, followed by a standard UAE procedure performed by an interventional radiologist.

All patients received a single dose of anti-biotics, conscious sedation, local anaesthetic at the access point and standardized intra-procedural analgesia (intravenous anti-inflammatories, cortisol, paracetamol, and opioids) as part of the standard UAE procedure.

Both uterine arteries were selected and embolized with 300- to 1000-micrometre polyvinyl alcohol particles or trisacryl gelatin microspheres designed for embolisation.

All patients who were treated between September 2017 and November 2019 received intra-arterial lignocaine as adjunctive analgesia as part of the practices updated UAE protocol.

A total of 10 ml 1% lignocaine (100mg), suitable for intra-vascular use, was injected into the embolised uterine artery, 50 mg on each side.

The pre and post operative analgesic regime was unchanged for the Control and Study group which included anti-inflammatories, paracetamol and two types of opioids. Additional analgesia, if required, was prescribed and documented by nursing staff. The patients were all visited by the

qualified interventional radiologist at the end of the day. Patients from both groups therefore were visited between 1 hour to 6 hours post procedure. Pain was documented on a standardized 11-point pain scale (0 representing 'no pain at all' and 10 representing 'excruciating'). During the post-procedure round patients were also assessed for nausea, vomiting and constipation, that was recorded as mild, moderate or severe.

All the patients who did not experience any post procedure complications were discharged either the same day or the following morning with analgesia and standard post-UAE procedure guidelines, which included instructions on what to expect after the procedure, and when to seek medical help.

Statistical Analysis

One-way Analysis of Variance (ANOVA) was used to compare average pain scores between the groups. Summary statistics were obtained by reporting means and standard deviations. Assumptions were checked as part of the ANOVA analyses and where necessary, the non-parametric Mann-Whitney U test was applied. A 5% significance level ($p < 0.05$) was used for determining significant results.

Ethical Consideration

Ethical approval to conduct the study was obtained from the Faculty of Health Sciences Human Research Ethics Committee of the University of Cape Town (HREC reference number: 836/2019) and the hospital.

Results:

A total of 473 patients met the inclusion criteria for the study during the overall observation period. 142 patients (30%) who presented before the introduction of intra-arterial lignocaine as adjunctive analgesia (Control group from July 2016 to September 2017), were compared with 331 patients (70%) who received intra-arterial lignocaine (Study group from September 2017 to November 2019).

In the Control group the patients' age ranged from 24-52 years old with an average age of 39 years (standard deviation of 6.3 years), whilst the Study group's age ranged from 17-57 years old with an average age of 38 years (standard deviation of 6.5 years). Most patients were between 30 and 50 years of age.

The most common complaint for women seeking help were menorrhagia (78%) and dysmenorrhoea (70%), followed by pressure symptoms (18%) and 10% for each infertility, dyspareunia and anaemia. (Fig 1)

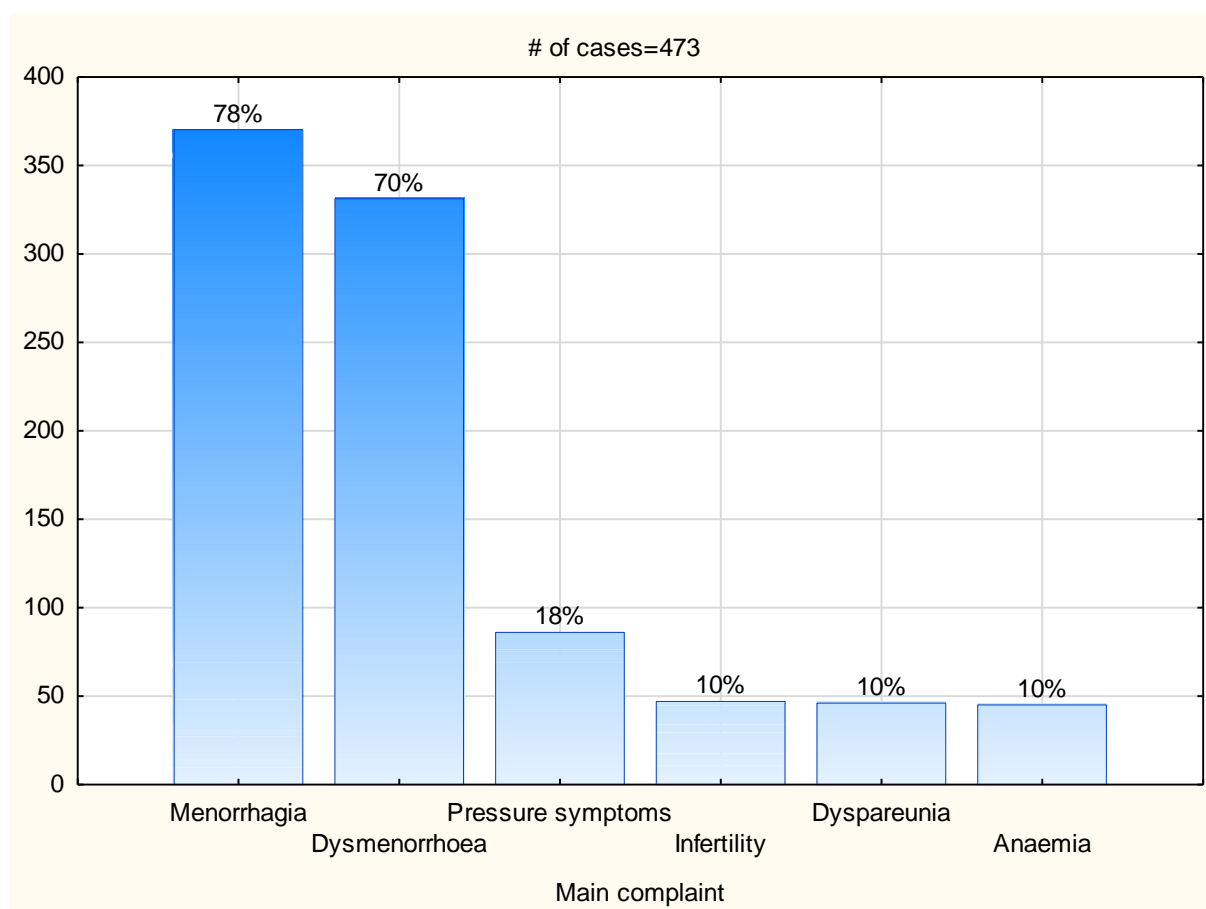


Figure 1 - Symptoms of Uterine Fibroids

Femoral artery access was the exclusive route in the Control group (n=142, 100%) with 92% of patients in the Study group receiving radial artery access (n=306)

Most patients in both groups were admitted for one day. There was a significantly higher percentage of patients who were admitted for two days in the Control group, (34%) compared to the Study group (19%), ($p < 0.01$). One patient from the Study group was discharged on the same day as the procedure.

There was no significant difference observed in the Visual Analogue Scale (VAS) pain scores between the two groups on the same day, next day or two days after the procedure. (Fig 2).

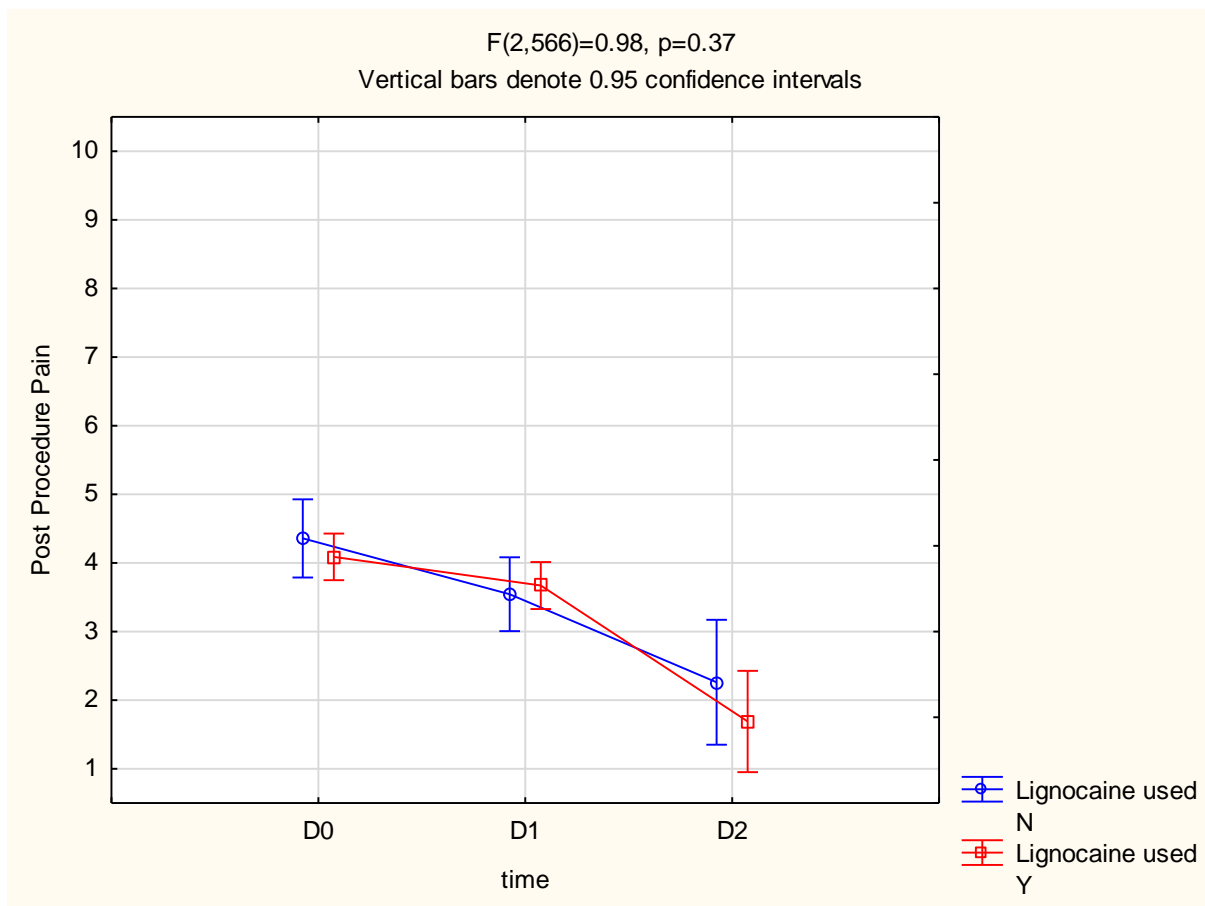


Figure 2 - Post procedural Pain

Although most patients reported feeling only minimally nauseous after the procedure, there was a statistically significant difference between the two groups with the Control group reporting more nausea on the day of the procedure (Day 0) ($p < 0.01$). (Fig 3).

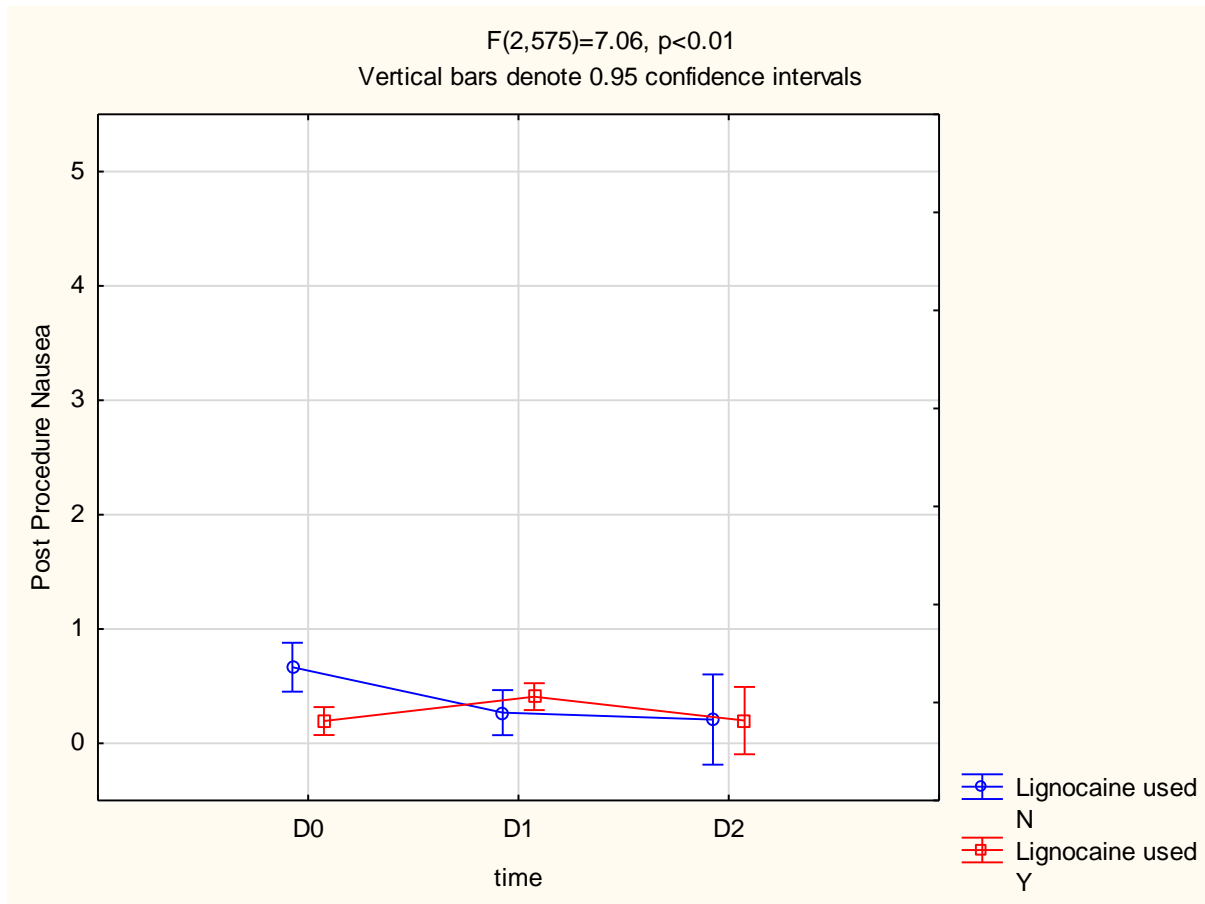


Figure 3 - Post procedural Nausea

None of the patients reported “moderate” or “severe” nausea with no significant difference between the two groups.

Of the patients who remained in hospital by day 2, the Control group had significantly higher complaints of “mild” to “moderate” constipation compared to the Study group ($p < 0.01$). (Fig 4)

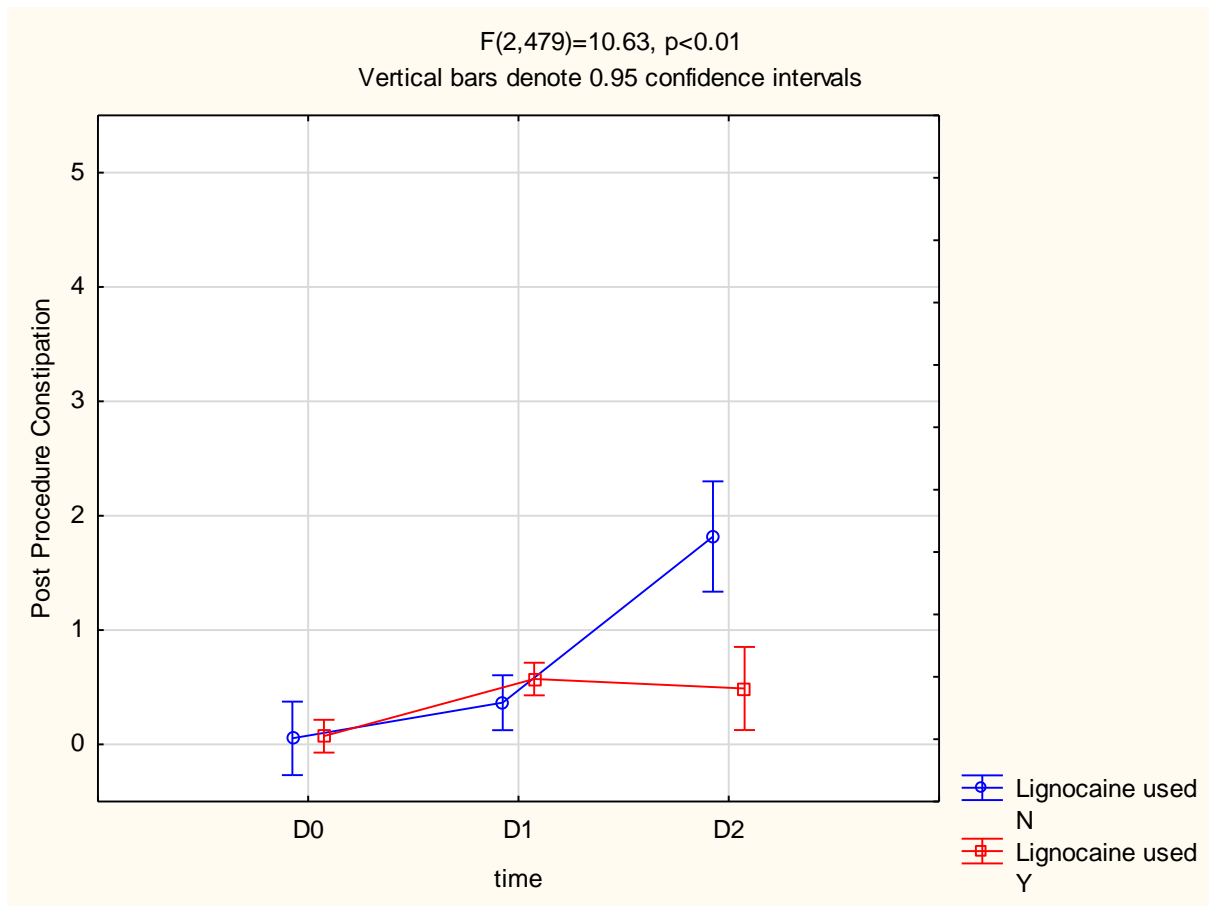


Figure 4 - Post procedural Constipation

From the total study population, only 40 patients (8.5%) required additional analgesia in the ward. There was a slightly higher incidence of additional analgesia in the Control group, 18 patients (12.7%) compared to the Study group, 22 patients (6.7%), $p=0.05$. Diclofenac was the mostly used post procedural analgesic of choice followed by Oxycodone and Pethidine.

There were no adverse events from the use of intravenous lignocaine during the study period.

Discussion:

Our study involving symptomatic uterine fibroids prevalent in women of late child-bearing age showed that the most common symptoms leading to women seeking help were menorrhagia and dysmenorrhea.

Post UAE intra-arterial lignocaine is held to be a safe and effective adjunctive analgesic within the early hours following UAE ^{3,9,11}.

Intra-arterial lignocaine administration is more effective when given after successful embolisation of the uterine arteries. When given before UAE, lignocaine can induce arterial spasm, apart from catheter induced vasospasm, and subsequently reduce fibroid infarction rate. ^{3,4}

Vasospasm of the arteries are hypothesized to be due to a transient local endothelial effect of the administered lignocaine and appears to be dose related rather than a peripheral or central-nervous system effect. The effects of vasospasm are thought to be pronounced in the sensitive uterine arteries due to their inherent physiologically need to contract during pregnancy. ^{3,4}

Studies have shown noteworthy differences in the VAS pain scores within four hours after lignocaine administration for UAE. ^{3,9,10} Duvnjak et al (2020) noted a significant difference in the pain scores after two hours ($p < 0.02$) whilst Noel-Lammy et al (2017) showed significant differences after four hours ($p < 0.01$). These studies did not demonstrate any significant difference in pain, 7 to 24 hours after lignocaine administration

Our results are comparable to literature which have not been able to demonstrate any significant difference in pain scores after 7 to 24 hours following lignocaine administration.

This significant finding in VAS pain scores is likely due to the fact that the maximal effect of lignocaine is within the first four hours after drug administration with a drug half-life of 90 to 120 minutes. ^{9,10}

In our study, the lignocaine dose administered was within the range of 100mg and 200mg as used by most authors. This is far below the sub-convulsive dose of 750 mg and the toxic range of 880 to 1040 mg IVI. ^{4,11}

There is however little consensus on the ideal dose of lignocaine to be used. Some authors have shown significant pain improvement with as little as 40 mg, ¹² while other have shown no pain improvement using 80 mg. ¹⁰

Intra-arterial administration of the short acting local anaesthetic, lignocaine, has timeously been proven to be safe following various procedures. All local anaesthetics carry a risk of systemic toxicity and appears to correlate to the degree of lipid solubility. Longer acting local anaesthetics, eg. Bupivacaine, are more lipid soluble and thus have an increased risk of systemic toxicity. Intravascular use of longer acting local anaesthetics are therefore discouraged with the risks outweighing the benefits.¹³

Although our study was not able to show a difference in pain scores between the two groups, adjunctive lignocaine during UAE was associated with reduced additional analgesic usage, as well as shorter hospital stays. In addition, our Study group reported less post procedural nausea and constipation. These may likely be attributable to the anti-inflammatory properties of lignocaine and decreased additional analgesic requirements.

Future studies with more frequent pain scoring, especially in the first 4 hours after the procedure may be able to demonstrate the pain improving properties of intra-arterial lignocaine more accurately. There is not yet a consensus on the dose of lignocaine to administer and future studies could examine this.

Following the study, the authors suspended the use of intra-arterial lignocaine and have implemented hypogastric nerve block of which the preliminary pain scores show promising results.

Study Limitations:

Our study was limited by the retrospective nature of the study and the non-randomization of our study population over the three-year study period. Therefore, an accurate contemporaneous analysis could not be performed. Although randomization of the study population would have been beneficial, the study population did represent patients with similar ages, and the procedure and analgesia protocols were standardized.

The study could have benefited from the use of set time intervals to collect post-procedural pain score assessments within the first 2 to 4 hours after the procedure.

Of note, practice protocol changed with radial access being the predominant access in the study group which may have had an impact on the study.

Operators not being blinded to the administration of adjunctive lignocaine could lead to bias.

The size of the uterine fibroids could play a role in the post procedure pain. Corresponding uterine and fibroid volumes and sizes were not collected as part of this study.

The use of different embolic material may have confounded interpretation of data as PVA particles are thought to cause an increased inflammatory response but how this relates to post operative pain remains questionable.¹⁴

Conclusion:

UAE for fibroids is known to be a painful procedure. Many drug protocols have been proposed to improve the patient's post-procedural experience. Our study showed no significant improvement in post-procedural pain scores following intra-arterial lignocaine administration. However, intra-arterial lignocaine administration did appear to have benefits of reducing the need for additional post-procedural analgesics, decreased post procedural nausea, less perceived constipation, and shorter hospital stay.

Acknowledgements:

Professor M Kidd (Department of Statistics, University of Stellenbosch) – statistical support

Competing Interest:

The authors declare they have no financial or personal conflicts to declare.

Author's contribution:

GP Human was the lead author, G Sudwarts was the supervisor, MJ Wojno was the co-supervisor

References:

1. Rischbieter P, Sinclair C, Lawson A, Ahmad S. Uterine artery embolisation as an effective choice for symptomatic fibroids: Five-year outcome. *South African J Radiol.* 2016;20(1):5 pages. doi:10.4102/sajr.v20i1.959
2. Prollius A, De Vries C, Loggenberg E, et al. Uterine artery embolization for symptomatic fibroids. *Int J Gynecol Obstet.* 2004;84(3):236-240. doi:10.1016/j.ijgo.2003.09.006
3. Noel-Lamy M, Tan KT, Simons ME, Sniderman KW, Mironov O, Rajan DK. Intraarterial Lidocaine for Pain Control in Uterine Artery Embolization: A Prospective, Randomized Study. *J Vasc Interv Radiol.* 2017;28(1):16-22. doi:10.1016/j.jvir.2016.10.001
4. Keyoung JA, Levy EB, Roth AR, Gomez-Jorge J, Chang TC, Spies JB. Intraarterial Lidocaine for Pain Control after Uterine Artery Embolization for Leiomyomata. *J Vasc Interv Radiol.* 2001;12(9):1065-1069. doi:10.1016/S1051-0443(07)61592-9
5. Lawson A, Cluver C, Olarogun J, et al. Uterine artery embolisation for uterine leiomyomas. *S Afr J Obstet Gynaecol.* 2014;20(1):18-21. doi:10.7196/SAJOG.798
6. Bulman JC, Ascher SM, Spies JB. Current Concepts in Uterine Fibroid Embolization. *RadioGraphics.* 2012;32(6):1735-1750. doi:10.1148/rg.326125514
7. Schirf BE, Vogelzang RL, Chrisman HB. Complications of uterine fibroid embolization. *Semin Intervent Radiol.* 2006;23(2):143-149. doi:10.1055/s-2006-941444
8. Lampmann LE, Lohle PN, Smeets A, et al. Pain management during uterine artery embolization for symptomatic uterine fibroids. *Cardiovasc Intervent Radiol.* 2007;30(4):809-811. doi:10.1007/s00270-007-9069-7
9. Duvnjak S, Andersen PE. Intra-arterial lidocaine administration during uterine fibroid embolization to reduce the immediate postoperative pain: a prospective randomized study. *CVIR Endovasc.* 2020;3(1). doi:10.1186/s42155-020-0099-4
10. Katsumori T, Miura H, Yoshikawa T, Seri S, Kotera Y, Asato A. Intra-Arterial Lidocaine Administration for Anesthesia after Uterine Artery Embolization with Trisacryl Gelatin Microspheres for Leiomyoma. *J Vasc Interv Radiol.* 2020;31(1):114-120. doi:10.1016/j.jvir.2019.09.007

11. Liu S, Li W. Intra-arterial lidocaine for pain control after uterine artery embolization: a meta-analysis of randomized controlled trials. *J Matern Neonatal Med.* 2020.
doi:10.1080/14767058.2020.1847079
12. Zhan S, Li Y, Wang G, Han H, Yang Z. Effectiveness of intra-arterial anesthesia for uterine fibroid embolization using dilute lidocaine. *Eur Radiol.* 2005;15(8):1752-1756.
doi:10.1007/s00330-005-2686-0
13. Butterworth JF, Lahaye L. *Clinical Use of Local Anesthetics in Anesthesia - UpToDate.* (Maniker R, Crowley M, eds.). Waltham, MA: UpToDate; 2021.
https://www.uptodate.com/contents/clinical-use-of-local-anesthetics-in-anesthesia?search=localanaesthetic&source=search_result&selectedTitle=2~148&usage_type=default&display_rank=1. Accessed October 4, 2021.
14. Han K, Kim SY, Kim HJ, et al. Nonspherical Polyvinyl Alcohol Particles versus Tris-Acryl Microspheres: Randomized Controlled Trial Comparing Pain after Uterine Artery Embolization for Symptomatic Fibroids. <https://doi.org/10.1148/radiol2020201895>. 2020;298(2):458-465. doi:10.1148/RADIOL.2020201895