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The rationale, design, and methods of a randomized, controlled trial to evaluate the efficacy of single-dose dexamethasone in reducing post-embolization syndrome in patients undergoing uterine artery embolization

Melinda Wang[a], Maureen P. Kohi[b,*]

[a] Weill Cornell Medical College, New York, NY, United States
[b] University of California San Francisco, San Francisco, CA, United States

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ABSTRACT

Background: Uterine artery embolization (UAE) is a minimally invasive technique well established for treating symptomatic uterine fibroids. However, the post-procedure recovery for UAE involves a notable inflammatory process in response to ischemia known as post-embolization syndrome (PES). PES encompasses transient leukocytosis, low-grade fever, and can result in readmission of up to 10% of patients. In surgical settings, multiple studies have demonstrated the efficacy of glucocorticoids in reducing inflammation and associated pain. However, this approach has not yet been assessed in predominantly ischemia-driven PES.

Methods: This paper describes the protocol of a prospective randomized, double-blind, placebo-controlled, multi-center trial to test the efficacy and safety of single-dose dexamethasone on inflammatory responses, pain, nausea, and readmission rates after UAE. The study will enroll pre-menopausal patients between 25 and 55 years (planned enrollment, n = 60) with MRI confirmed symptomatic fibroids. Patients will be randomly allocated into two groups: single-dose intravenous dexamethasone plus standard of care or placebo (normal saline) plus standard of care.

Results: The primary endpoint is the patient pain score 4 h following the UAE procedure. Secondary endpoints include pain scores at 7 h and 24 h following UAE; narcotic usage in the first 24 h following UAE; and serum inflammatory markers (white blood cell count, C-reactive protein [CRP], interleukin-6 [IL-6], and cortisol) 24 h after UAE.

Conclusion: Given the high incidence of post-procedure pain and difficulty with pain control after uterine artery embolization, results of this trial may directly influence the standard of care in perioperative management of patients undergoing UAE.

1. Introduction

1.1. Background

Uterine fibroids are the most common benign neoplasm of the female pelvis and result in symptoms of heavy menstrual bleeding, pelvis pressure/bulk, pain, and infertility [1]. Uterine artery embolization (UAE) is a well-established, minimally invasive treatment option for symptomatic uterine fibroids, with comparable long-term symptom relief, health-related quality of life, and patient satisfaction reported when compared to hysterectomy or myomectomy [2–5]. However, the post-procedure recovery for UAE involves a notable inflammatory process, with transient leukocytosis, fatigue, low-grade fever, lack of appetite, nausea, and vomiting. 86% of women treated with UAE demonstrate an increase in white blood cell count (WBC) in the first 24 h post-procedure [6]. Pain associated with the procedure is thought to be related to these inflammatory processes. Collectively, these symptoms are known as post-embolization syndrome (PES) and can result in readmission of up to 10% of patients, adding extraneous burden on the healthcare system [6,7].

The perioperative use of epidural analgesia [8], superior hypogastric nerve blocks [9,10], or intraarterial lidocaine [11,12] to control PES has been described. Current standard of care controls pain with nonsteroidal anti-inflammatory drugs (NSAIDs) as an adjunct to opioids. However, NSAIDs only inhibit the vascular phase of inflammation, reducing vasodilation and vessel wall permeability [13]. Glucocorticoids are considered to be more potent anti-inflammatory agents by inhibiting both the vascular phase and the cellular phase

* Corresponding author. 505 Parnassus Avenue, M-361, San Francisco, CA, 94143, United States.
E-mail address: Maureen.Kohi@ucsf.edu (M.P. Kohi).

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(leukocyte extravasation) of inflammation. By further reducing the inflammatory response secondary to ischemic changes, pain may also be better alleviated.

Multiple studies have demonstrated the efficacy of perioperative glucocorticoids, particularly dexamethasone, in reducing inflammation and pain in surgical settings [14]. By inhibition of the NF—kB pathway and upregulation of anti-inflammatory mediators such as IL-1 and NEP, glucocorticoids cause a substantial anti-inflammatory effect and are used in various autoimmune and inflammatory conditions.

1.2. Rationale and objectives

The use of dexamethasone in reducing post-operative inflammation and symptoms of PES after UAE has not been described extensively, with insufficient randomized controlled trial data. In addition, previous studies have been limited by lack of evaluation for resolution of fibroid symptoms or long-term follow-up to assess for readmissions or adverse events [14,15]. Given the high incidence of post-procedure pain and difficulty with pain control after UAE, our objective is to investigate the effects of single-dose intravenous (IV) dexamethasone on inflammatory responses, pain, nausea, and readmission rates after UAE. If proven that a single pre-procedure dose of dexamethasone can reduce pain and the inflammatory response, all patients undergoing UAE may benefit from this change in medical management.

2. Materials and methods

2.1. Overview

The UAE-dex study is a prospective randomized, double-blind, placebo-controlled, multi-center trial in patients undergoing UAE for the treatment of symptomatic uterine fibroids. A total of 6 sites will participate in this study, with no site enrolling more than 15 patients. The sites include: University of California, San Francisco, Stanford University, University of California, Irvine, University of Colorado, Denver, Georgetown University, and Miami Cardiac and Vascular Institute.

2.2. Eligibility criteria and randomization

The study will include pre-menopausal women between the ages of 25–55 years with symptomatic uterine fibroids confirmed by recent MRI. Each patient must also be able to provide informed consent and participate in all study activities. Exclusion criteria include history of pelvic malignancy, viable pregnancy, active pelvic infection, severe contrast allergy, or renal insufficiency. Due to exposure to fluoroscopy, patients with viable pregnancies will not be included in this study. Similarly, patients who report a serious allergic reaction to contrast agents as well as patients with renal insufficiency (serum creatinine > 1.5 mg/dL) will be excluded. Patients with active pelvic infection are not included due to relative contraindication of dexamethasone use.

Randomization will take place prior to the embolization procedure and will determine if the subject receives a single dose of dexamethasone or placebo (normal saline) prior to the UAE procedure. Block randomization will be used to ensure a balance in sample size across groups during the course of study enrollment [16]. The study coordinator at each site will record the randomization number on all documents. Because of the double blinded nature of the study, the study coordinator will communicate whether the patient has been randomized to receive dexamethasone or placebo to another interventional radiology physician who is not part of the study. This physician will then ensure that the subject receives either dexamethasone or placebo without the knowledge of the treating interventional radiologists. Subjects will be blinded to whether they received dexamethasone or placebo.

2.3. Outcomes

Patients will be assigned randomly to the treatment group (single pre-procedure dose of dexamethasone) or the control group (normal saline). The primary objective of this study is to evaluate the effect of a single-dose of IV dexamethasone and pain and inflammatory response following UAE. The primary endpoint is the patient pain score 4 h following the UAE procedure.

Secondary endpoints will include pain scores at 7 h and 24 h following UAE; narcotic usage in the first 24 h following UAE; and serum inflammatory markers (white blood cell count, C-reactive protein [CRP], interleukin-6 [IL-6], and cortisol) 24 h after UAE. Additional endpoints include change of symptom severity and quality of life evaluated with the Uterine Fibroid Symptom and Health-Related Quality of Life Questionnaire (UFS-QOL) and an imaging endpoint of the change in the volume of the uterus and dominant fibroid and extent of fibroid necrosis determined on MRI pelvis performed 3 months after the UAE.

The estimated timeline for this study is 12 months. The study will be halted when sufficient data for the primary endpoint are gathered and an interim analysis can be performed.

2.4. Power analysis

The primary outcome of this study is the pain score 4 h following the UAE procedure. With 60 patients randomized 1:1 to the two treatment arms, the two-sided two-sample *t*-test has sufficient (93%[80%]) power to detect a difference observed in prior study of 35 ± 22.6 vs. 59.4 ± 30.3 at the 0.05 [0.0085, Bonferroni adjustment for multiple testing] significance level. This study is sufficiently powered to detect an effect size of 0.5*SD at the two-sided 0.05 significance level and 1*SD at the two-sided 0.05/10 significance level. Effect of this magnitude was observed in a prior study in WBC count. Analyses anticipate 15% drop-out rate (see Fig. 1) (see Table 1).

2.5. Pre-treatment assessment

Each subject will be seen in a clinic setting by an interventional radiologist prior to enrollment. During the visit, the physician will determine if the patient meets the inclusion criteria to be included in this clinical trial. Informed consent, medical and surgical history, medication history, physical examination, and laboratory values, including complete blood count (CBC), prothrombin time and international normalized ratio (PT/INR), and serum creatinine, will be completed at this time. The UFS-QOL will also be administered at this time to assess for presenting symptoms and effect on quality of life. A baseline contrast-enhanced pelvic MRI will be performed. A summary of all study activities can be found in Table 2 and a timeline in Fig. 2.

Table 1
Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
30–50 years of age at enrollment	History of pelvic malignancy
Pre-menopausal	Viable pregnancy
Able to provide informed consent	Active pelvic infection
Uterine fibroids documented by MRI	Sever contrast allergy
Symptomatic uterine fibroids causing one or more symptoms such as: heavy menstrual bleeding, bulk symptoms with bladder or bowel dysfunction or abdominal protrusion, dysmenorrhea, dyspareunia, infertility	Renal insufficiency