

Oxytocin Administration Improves Efficiency of HIFU Treatment of Uterine Fibroids

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ABSTRACT

Purpose: We aimed to investigate whether there was any benefit of administrating oxytocin during magnetic resonance-guided High-Intensity Focused Ultrasound (HIFU) treatment of uterine fibroids.

Methods: Forty women who underwent HIFU ablation of uterine fibroids were divided into two groups, one received IV oxytocin infusion during the procedure and the other did not. The total energy used and sonication time required to reach 60°C as well as acoustic energy for increasing 1°C of temperature at the single point were noted. In addition, MR measures including initial and final perfused volume of fibroid as well as the mean fibroid volume change after 6 months were evaluated. All data were compared between the two groups.

Results: The average total sonication energy required to reach 60°C and the energy required for increasing 1°C at a single point were both significantly greater in the patients who did not receive oxytocin. It also took much longer to sonicate a single point in this group ($p < 0.01$). The non-perfused volume measured at the end of the procedure as well as mean change in fibroid volume measured six months later were both significantly larger in patients with oxytocin administration ($p < 0.05$). The remaining parameters did not show significant difference between both groups.

Conclusion: Oxytocin administration improves efficiency and efficacy of HIFU ablation of uterine fibroids.

Keywords: HIFU; Uterine fibroid; Oxytocin

INTRODUCTION

Uterine fibroids are the most common benign, hormone-sensitive smooth-muscle tumors [1-3]. They are found in at least 40% of all women and thus cause a significant healthcare and social problem because of symptoms such as heavy bleeding, anemia, pain and increased size of the abdomen as well as major fertility and pregnancy complications [4]. In the past, the only way for managing patients with uterine fibroids was surgical excision (myomectomy) or sometimes even hysterectomy. Many patients refuse this because of fear of surgery and its consequences. Myomectomy is associated with the risk of uterine penetration which can induce adhesions and subsequent infertility, while hysterectomy causes irreversible sterilization [1-4].

High-intensity focused ultrasound (HIFU) ablation is an emerging safe and non-invasive therapeutic modality that

induces necrosis of biological tissues by focusing high-energy ultrasound waves onto one small spot [5]. It is increasingly being used to treat uterine fibroids all over the world because of its notable safety profile and considerable therapeutic efficacy [5]. HIFU exerts its effect by heating tumor tissue causing irreversible coagulative necrosis [6,7]. The degree of induced heating is influenced by several internal and external factors that include the relative composition of smooth muscle cells and collagen fibers of the uterine fibroids [8] and subcutaneous fat layer of the abdominal wall among others [9]. A very important influencing factor for heating is the degree of vascularity of the uterine fibroids. The greater the vascularity of the fibroid, the more difficult it is to elevate the temperature of the tumor cells [10]. Thus decreasing fibroid vascularization can potentially facilitate HIFU procedures and improve the outcome.

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Oxytocin is a peptide hormone released by the hypothalamus. It acts directly on receptors located on the uterine smooth muscle cell during labour. This leads to myometrial contraction, involution of the uterus and closure of uterine blood vessels after delivery [11,12]. There are oxytocin receptors in the non-pregnant uterus as well, but their concentration is much lower than that found during pregnancy. This suggests a possible role for oxytocin in regulating vasomotor tone of the myometrial vasculature in addition to myometrial contraction. Further evidence for this are reports of decreased blood loss during both surgical and laparoscopic myomectomy with high-dose oxytocin infusion during the procedure [13-15].

In the current study we aimed to investigate whether intravenous (IV) administration of oxytocin during HIFU ablation of uterine fibroids would add any benefit warranting its routine use in all patients undergoing this procedure.

METHODS

Study design and participants

This is a comparative observational study that included 40 patients with solitary uterine fibroids who underwent HIFU treatment over a 12 month period in the HIFU Egypt Center. The patients were divided into two groups.

Without oxytocin group: The data for patients in this group were collected retrospectively. This is because at the time they had the procedure done; oxytocin administration was not part of the protocol implemented in our center.

Oxytocin group: The data for the patients in this group was collected prospectively as soon as oxytocin administration became part of our protocol during HIFU. Thus all those patients received oxytocin during the procedure.

The patients were collected consecutively until a total of 20 women with complete data sets and measures including follow up studies were included in each group. The inclusion and exclusion criteria were identical in both groups and the utmost care was taken to control for all variables to ensure that the only difference between the two groups was the administration of oxytocin during the procedure.

Inclusion criteria

- (a) Age 18-45 years,
- (b) Patients with symptomatic uterine fibroid measuring up to 10 cm in diameter,
- (c) Positive MR qualification (Funaki type I or II, suitable beam window),
- (d) American Society of Anesthesiologists (ASA) physical status 1-2 [16].
- (e) Platelet count $\geq 100,000/\text{mm}^3$,
- (f) Prothrombin concentration $>70\%$ and
- (g) Serum creatinine level $\leq 2.0 \text{ mg/dl}$.

Exclusion criteria

- (a) Lack of patient consent,
- (b) Pregnancy,
- (c) Calcified or predominantly degenerated fibroids,
- (d) History of allergy to topical anesthetics or narcotics,
- (e) History of chronic use of sedatives, narcotics, alcohol or illicit drugs,
- (f) Obese patients with thick abdominal wall fat layer,
- (g) Presence of a scar caused by previous surgery or trauma in the sonication path,
- (h) Patients with cardiac pacemakers,
- (i) Patients previously subjected to radiotherapy involving the thoracic wall/cavity, and
- (j) Mentally challenged patients.

The study was approved by the local ethics committee and informed written consent was obtained from each patient.

HIFU Protocol

All patients had the procedure done under conscious sedation using a US-guided HIFU (USgHIFU) tumor therapeutic system [JC or JC200, Chongqing Haifu (HIFU) Tech Co., Ltd., Chongqing, China]. The built in B-mode ultrasound device (MyLab 70, Esaote, Genova, Italy) was used to provide real-time imaging for monitoring and targeting the lesions. The transducer of 20 cm in diameter worked at a frequency of 0.8-1.2 MHz and produced energy of 400 W. The focal length was 150 mm, and the dimensions of focal region were 1.5 mm-1.5 mm-10 mm.

Bowel preparation was performed by all patients before HIFU treatment. This included intake of liquid food for 3 days, fasting for 12 hours pre-treatment and a cleansing enema 2-4 hours prior to the procedure. Skin preparation involved shaving of the hair on the abdominal wall from the umbilicus to the upper margin of the pubic symphysis, and then cleaning the area with 70% ethanol. The area was also degreased and degassed water to remove oils from the skin before procedure. Insertion of a urinary catheter into the bladder was done to control the bladder volume and optimize the therapeutic acoustic pathway.

A degassed water balloon was used to compress and push away bowels from the acoustic pathway and prevent intestinal injury. The patients were placed in prone position on the HIFU therapeutic system table with the anterior abdominal wall in contact with degassed water. Dynamic real-time ultrasonographic imaging was used to observe the target area and the adjacent tissue. The patients were asked to report any discomfort and vital signs were monitored. The therapeutic energy was adjusted based patient feedback and changes in gray scale on ultrasonographic imaging. This process was repeated on a section-by-section basis to achieve complete ablation of the planned ablation area.

The procedure was terminated when the hyperechoic area covered the entire treated lesion or colour Doppler ultrasound imaging showed no blood supply. Immediately after HIFU ablation, gadolinium-based contrast-enhanced MR imaging was performed to evaluate the treatment results. This was also done six months later. After the procedure, each patient lay in prone position for 2 hours in the observation room after which they were discharged provided no serious complications occurred. Oral antibiotics were prophylactically prescribed for 3 days. Each complication was recorded as it occurred during and after the treatment until 4 weeks after the procedure and the patients were instructed to contact the center immediately if any issues occurred.

Anesthetic procedure

All patients in both groups: Initially, all baseline data (age, sex, vital signs) were recorded while the patients were being prepared for the procedure. An IV line was inserted and saline infusion (500 ml/hour) was administered. Standard monitoring (i.e. pulse oximetry, automated non-invasive blood pressure measurement, and electrocardiography) was performed. The patients received 2 L of prophylactic 100% oxygen supplementation through a nasal cannula and received an initial bolus of 100 to 150 µg/kg of midazolam and 1 to 2 µg/kg fentanyl administered with weight based and sedative-level limitations.

The initial dose for induction was administered in the same way both times and maintenance doses were administered according to the infusion method. Maintenance of anesthesia was achieved with intermittent boluses of, midazolam hydrochloride, 20-30 µg/kg and fentanyl, 0.8-1 µg/kg, repeated at 30-40 minute intervals.

Anesthesia was maintained using continuous infusion of 25-50 µg/kg/hour midazolam and 0.5-1 µg/kg/hour fentanyl. The infusion rate was increased or decreased in 10 µg/kg/hour midazolam and 0.05 µg/kg/hour fentanyl increments. An increase in the infusion rate was done when signs suggestive of a lightening of the anesthetic state occurred (see above). Conversely, it was decreased when there were signs suggestive of an excessively deep anesthetic state (decreased respiratory rate, hypotension).

Table 1: Patient and fibroid characteristics (Mean ± SD).

Variable	Without oxytocin group (n=20)	Oxytocin group (n=20)
Age (years)	32.9 ± 6.3	34.1 ± 9.1
Height (cm)	158.9 ± 11.6	160.6 ± 7.8
Weight (kg)	79.2 ± 12.1	82.4 ± 10.4
Mean abdominal wall Thickness (mm)	30.3 ± 10.9	31.8 ± 13.2
Mean uterine wall volume (cm ³)	241.2 ± 31.1	238.9 ± 44.3

Extra bolus injections of midazolam, 10-50 µg/kg, and/or fentanyl, 0.5 µg/kg were administered, if necessary, in both procedures to maintain blood pressure within 20% of baseline or if inadequate anesthesia was determined.

Oxytocin protocol (Oxytocin group only): For group A, 2 ampules of oxytocin (10 µ/mL/amp) were added to normal saline solution 1000 mL and run with intravenous infusion at a rate of 120 mL/hour. Intravenous oxytocin infusion was stopped immediately after the end of the surgery.

Assessment modalities

Identical assessment was carried out for each patient in both groups. The following MR measures were obtained:

Before the procedure: The mean fibroid volume (MFV) and initial perfused volume (IPV).

During the procedure: Total energy required for sonication to reach 60°C at the single point; time for sonicating a single point and acoustic energy for increasing 1°C of temperature at the single point.

After the procedure: Final perfused volume (FPV) and nonperfused volume (NPV) was calculated (NPV=FPV-IPV).

Six months after the procedure: Mean fibroid volume change (MVC).

Statistical analysis

Data collected are described in detail under results. After checking for the normality of the data distribution student's two tailed t-test was used for comparison of variables between the two procedures and a p value<0.05 was considered significant.

RESULTS

Clinical and demographic characteristics are shown in Table 1. No significant differences were found between the two groups and they were comparable in terms of demographic and clinical characteristics as well as the procedure performed. All the patients tolerated the treatment session well with no report of any significant side effects related to the procedure. They all left the center the same day and no hospitalization was required for any.

Dominant fibroid tumor type (number of patients)		
Submucosal	5	5
Intramural	13	14
Subserosal	2	1
Dominant fibroid tumor location (number of patients)		
Anterior wall	13	12
Posterior wall	5	6
Lateral wall	1	0
Fundus	1	2

As illustrated in Table 2, there was no difference in the mean fibroid volume or total ablated tissue volume between the groups. However, the average total sonication energy required to reach 60°C (p<0.01) as well as the energy required for increasing 1°C at a single point (p<0.01) were both significantly greater in the patients who did not receive oxytocin. It also took much

longer to sonicate a single point in this group (p<0.01). Furthermore, the non-perfused volume (NPV=FPV-IPV) measured at the end of the procedure as well as mean change in fibroid volume measured six months later were both significantly larger in patients with oxytocin administration (p<0.05).

Table 2: MR and sonication measures (Mean ± SD, *p<0.05, **p<0.01).

Variable	Without oxytocin group (n=20)	Oxytocin group (n=20)
Procedure time (min)*	102.3 ± 25.1	90.8 ± 14.4
Mean fibroid volume (ml)	92.9 ± 21.3	95.7 ± 19.9
Total energy required for sonication to reach 60°C at the single point (J)**	5784.5 ± 1056	3104.2 ± 571
Time for sonicating a single point (sec)**	25.2 ± 15.7	11.9 ± 7.2
Acoustic energy for increasing 1°C of temperature at the single point (J)**	347.9 ± 98.5	141.2 ± 87.1
Non perfused volume (ml)*	67.5 ± 11.7	52.1 ± 8.9
Mean fibroid volume change (%)*	42.2 ± 7.3	76.5 ± 9.6

DISCUSSION

HIFU ablation causes irreversible coagulative necrosis as a result of protein denaturation when the tumor tissue receives a thermal dose beyond a certain degree (lethal thermal dose). This dose is achieved instantaneously (within 1 to 2 seconds) if a temperature of 56°C-60°C is used thereby killing the tumor cells [6,7]. One of the most important factors that influence the degree of induced heating during HIFU ablation of uterine fibroids is the degree of vascularity of the uterine fibroids [17]. The rise in temperature induced by hyperthermic therapy becomes more difficult as the vascularity of the treated tumor increases [10]. It is therefore difficult to elevate the temperature of highly vascularized fibroids, as they require higher acoustic energy to induce appropriate heating [5]. Accordingly, contraction of uterine muscle and blood vessels can potentially

decrease blood flow which may lead to better results in HIFU therapy.

Our results suggest that IV oxytocin can potentially help in regulating vasomotor tone of the myometrial vessels in the non-pregnant uterus and improve HIFU treatment outcomes. The average total sonication energy required to reach 60°C and the energy required for increasing 1°C at a single point were both significantly greater in the patients who did not receive oxytocin. It also took much longer to sonicate a single point in this group. This implies that addition of oxytocin during the procedure has a substantial effect on improving the efficiency of performing the procedure by decreasing the total energy and time required to ablate tumor tissue. Furthermore, the volume of ablated tissue (non-perfused volume) measured at the end of the procedure as well as the total volume change measured six

months later was much larger in patients with oxytocin administration during HIFU therapy. This parameter quantifies the degree of necrosis after treatment and thus the results show much better efficacy of treatment with oxytocin administration during the procedure.

Our findings are supported by the two other studies in which oxytocin was used during HIFU [18,19] as well as during both surgical and laparoscopic myomectomy [13-15]. It is likely that oxytocin administration caused vasoconstriction of the uterine vessels, thereby facilitating heating of the tumor tissue by HIFU [20]. Another possible mechanism may be contraction of the fibroid tissue with subsequent externalization of extracellular fluid which can also lead to more effective heating of the tumor tissue [19].

LIMITATION OF THE STUDY

One limitation of our study is that it was a combined retrospective and prospective analysis. While extensive measures were taken to ensure controlling for all factors between the groups, a large prospective study is probably the next step to validate the findings.

CONCLUSION

Our results are very promising and show great potential for IV oxytocin administration to significantly improve the efficiency and efficacy of HIFU ablation of uterine fibroids.

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