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ORIGINAL ARTICLE

Color Doppler Misoprostol Response Study (CDMRS): An Evaluation Tool for Patients Awaiting Myomectomy

Musarrat Hasan*, **Ayesha Nasir**, **Erum Saba**

Institute of Ultrasound Imaging Karachi, Pakistan

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color Doppler,
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Background: Uterine myomas (fibroids) are benign tumors of the uterus. Myomectomy, the surgical removal of myoma, is an important treatment option. The major complication associated with myomectomy is excessive bleeding. Many interventions have been used to reduce bleeding during myomectomy. Misoprostol produces uterine contraction, thereby reducing blood supply to the myometrium and in the myoma; it can be used as an alternative to uterine artery occlusion or paracervical tourniquet to reduce blood flow during myomectomy. The Color Doppler Misoprostol Response Study (CDMRS) is a study planned to assess the vascularity of the myoma in patients with fibroid uterus and note the changes after misoprostol administration.

Materials and methods: A baseline study of all the patients was done prior to insertion of misoprostol or placebo, and the largest selected fibroid in the patients with uterine fibroids was evaluated for its volume and perfusion by Doppler ultrasound. The resistive index (RI) was measured prior to and after administration of 800 μg misoprostol (4 tablets) per rectal insertion, after 20 minutes, and reevaluated 40 minutes postinsertion.

Results: Results from a *t*-test shows that the use of misoprostol significantly reduces the volume of fibroid from 0–20 minutes by t_{0-20} [mean difference = 40.3 cm^3, confidence interval (CI) 30.6–49.9, $p = 0.000$) and t_{20-40} (mean difference = 36.2 cm^3, 95% CI 30.7–41.6 cm^3, $p = 0.000$). In the control group receiving four tablets of placebo no significant difference was noted in volume of the fibroid. Likewise, when we compared the RIs at different timings, the results were again in favor of misoprostol because the blood flow of myomas was substantially reduced. The RI increased from t_{0-20} (mean difference = 0.26, 95% CI 0.16 cm^3–0.38 cm^3, $p = 0.000$) and t_{20-40} (mean difference = 0.08, 95% CI 0.33–0.04 cm^3, $p = 0.000$). In the control group receiving four tablets of placebo, no significant difference was noted in perfusion of the fibroid.

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* Correspondence to: Dr Musarrat Hasan, Director, Institute of Ultrasound Imaging, Room No 1, Hiala-e-Ahmer House, Main Clifton Road, Karachi Pakistan.

E-mail address: musarrat27@hotmail.com (M. Hasan).

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Conclusion: In conclusion, we suggest that all patients scheduled for myomectomy have prior CDMRS to evaluate the degree of vascularity and to assess if they have an appropriate response to misoprostol administered rectally, so that there is minimal or no blood loss during surgery. This preoperative assessment will decrease physician apprehension, with less intraoperative blood loss and morbidity.

Introduction

Uterine myomas (fibroids) are benign tumors of the uterus. Myomectomy, the surgical removal of myoma, is an important treatment option, especially for women who wish to preserve their uteri. The major problem with myomectomy is excessive bleeding, which can be life threatening and prolong hospital stay. Many interventions have been used to reduce bleeding during myomectomy. The effective ones include the use of tourniquets, vasopressin, chemical dissection, misoprostol, bupivacaine plus epinephrine, and tranexamic acid [1].

Mifepristone (the abortion pill) also has been shown to shrink uterine fibroids and improve quality of life [2].

Misoprostol, which is a prostaglandin analogue, is now being widely used in the prevention and treatment of postpartum hemorrhage as well as to induce birth or abortion [3]. By contracting the myometrial muscles, misoprostol has been shown to reduce the uterine artery blood flow [4]. This has been shown in Fig. 1 (A and B).

In vitro studies have shown that prostaglandins have a vasoconstrictive effect [5].

Previous studies have shown that uterine artery blood flow to the myometrium is increased in patients with myoma [6].

Uterine artery occlusion techniques developed as an alternative to the hysterectomy or myomectomy, and are successfully used in most myoma uteri cases [7,8]. Although a temporary effect, misoprostol can reduce blood flow in the myoma, and therefore can be used as an alternative to uterine artery occlusion or other invasive techniques to reduce blood flow during myomectomy [9].

The purpose of our Color Doppler Misoprostol Response Study (CDMRS) was to observe changes in vascularity and perfusion of fibroids and the surrounding myometrium following misoprostol per rectal administration (Fig. 2).

Materials and methods

To undertake this study, the ethical approval was taken from the Ethical Review Board of the Ultrasound Society of Pakistan (Fig. 3).

The study was conducted at the Clinic/Institute of Ultrasound Imaging, Karachi, Pakistan from March 2009 to November 2011. Our center is affiliated with Thomas Jefferson University Hospital, Philadelphia, PA, USA, and provides services to almost 25,000 patients per year. Ultrasound of almost every part of the body is done at our center with the facilitation of convex, linear, transvaginal, and three-dimensional probes. The procedures are being carried out by ultrasonographer specialists and the machine used for this work was Toshiba Xario SSA-660A with a 3.5 MHz standard convex probe.

All premenopausal women (age 20—40 years) having fibroids not less than 5 cm in diameter were included in the study. The patients were evaluated during the follicular phase of the menstrual cycle Day 8 to decrease the chances of ambiguity regarding endometrial thickness and general vascularity. Written informed consent was obtained from those who wished to participate in the study. Patients who had a body mass index greater than 30, a known allergy to misoprostol, hypertension, cardiac or pulmonary disease, or fibroids smaller than 5 cm in diameter were excluded from the study. We recruited 100 patients during the study period, which fulfilled the inclusion criteria, and who agreed to participate in the study.

This was a double-blind randomized trial. Every patient filled in baseline information prior to the procedure and

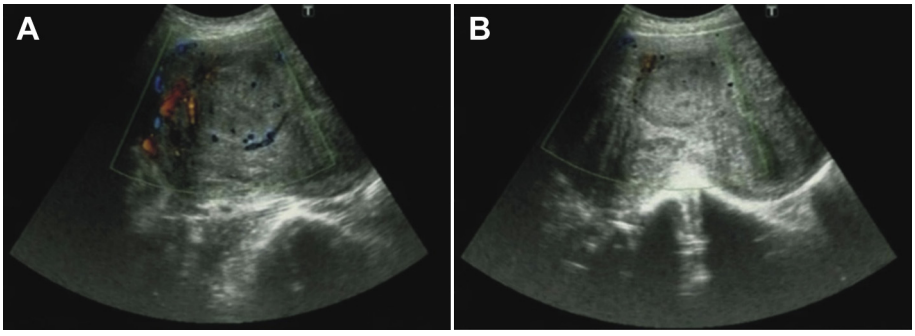

Fig. 1 Comparison of the change of blood flow in the myoma on Color Doppler Misoprostol Response Study (A) before and (B) after misoprostol administration.

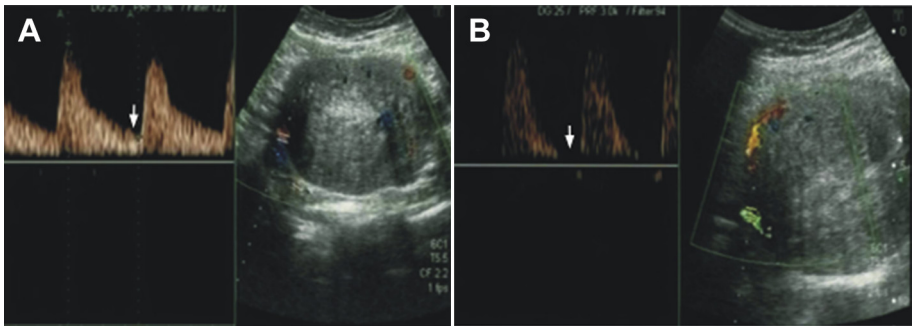

Fig. 2 Comparison of the change in spectral Doppler of the blood flow in the myoma (A) before and (B) after misoprostol administration.

had a transabdominal examination that was essential to adequately measure uterine size in women with a large uterus. We then divided the patients into two groups. The principal investigator along with the co-investigators performed the ultrasound prior to and after administering misoprostol. The patients in the study group ($n_1 = 50$) were given 800 μg misoprostol (4 tablets) rectally and those in the control group ($n_2 = 50$) received placebo (inert tablet in the same color and shape).

Myoma volume was expressed in cm^3 and was calculated according to the formula: length (cm) × depth (cm) × width (cm) × 0.5. If more than one myoma was found in the pelvis, the largest one was examined and the site localized by its distance from the endometrium and the serosa.

The myoma vascularization and that of the surrounding myometrium was visualized using the color Doppler technique. Blood flow velocity waveforms were obtained by placing the Doppler gate over the maximum color areas and activating the pulsed Doppler function at that marked site. The vessel was measured after confirming the depth (same depth of vessel from the upper margin) and the angle correction prior to and after insertion. Resistive index (RI) of the myoma vascularization was measured prior to and after 800 μg misoprostol (4 tablets) per rectal insertion, after 20 minutes, and again re-evaluated 40 minutes after insertion. All patients were followed up the next day to report any side effects.

Statistical analysis

We obtained frequencies of categorical variables, and for continuous variables mean and standard deviation were calculated. To determine whether misoprostol administration can change the volume of fibroids and level of RI at different time intervals, we used the paired *t*-test. The values were compared as (t_0 vs. t_{20}) and (t_{20} vs. t_{40}) at 0.05 level of significance. Data analysis was carried out using SPSS 19.0 (IBM, Armonk, NY, USA).

Results

The maternal demographic information along with the descriptive statistics, 95% confidence interval (CI) of volume of fibroid, and RI at different time intervals was analyzed. The average age of the women in the study group and in the control group was 36.04 ± 5.17 years and 36.1 ± 5.50 years, respectively. There were 6% primiparous and 47% multiparous women in both the groups.

Results from the *t*-test shows that the use of misoprostol significantly reduces the volume of fibroid from 0 minutes to 20 minutes by t_{0-20} (mean difference = 40.3 cm^3, 95% CI 30.6–49.9, $p = 0.000$) and t_{20-40} (mean difference = 36.2 cm^3, 95% CI 30.7–41.6 cm^3, $p = 0.000$). In the control group receiving four tablets of placebo, no significant difference was noted in the volume of the fibroid.

Likewise, when we compared the RIs at different times, the results were again in favor of misoprostol because they significantly reduced the blood flow of myomas. The RI increased from t_{0-20} (mean difference = 0.26, 95% CI 0.16–0.38 cm^3, $p = 0.000$) and t_{20-40} (mean difference = 0.08, 95% CI 0.33 cm^3–0.04 cm^3, $p = 0.000$). In the control group receiving four tablets of placebo, no significant difference was noted in perfusion of the fibroid. It was observed that 27 of the patients had absent flow within the fibroid at 20 minutes and 41 patients were found to have absent flow at 40 minutes (Tables 1 and 2).

Discussion

The standard treatment for symptomatic myomas is hysterectomy for women who have completed their families, and myomectomy for women who wish to preserve fertility. Myomectomy can be accomplished by laparotomy, laparoscopy, or hysteroscopy.

Massive blood loss associated with the dissection of huge fibroids renders myomectomy a more technically challenging procedure than hysterectomy. Transfusion is required in up to 20% of cases following abdominal myomectomy; in 2% of cases, there is a need for conversion of myomectomy to hysterectomy [10].

A number of interventions have been introduced to reduce bleeding during myomectomy. Three categories of interventions can be identified: (1) intervention on uterine arteries such as laparoscopic uterine artery dissection, uterine artery embolization, pericervical mechanical tourniquets, and hormonal tourniquets such as vasopressin and telipressin; (2) uterotonics such as ergometrine, oxytocin, misoprostol, and sulprostone; and (3) myoma dissection techniques that include the use of laser and chemical

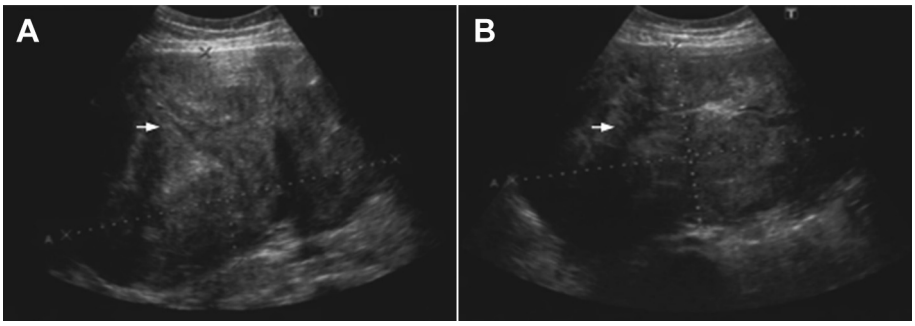

Fig. 3 Comparison of the change in the size of the myoma (A) before and (B) after misoprostol administration.

dissectors such as sodium mercaptoethanesulfonate (mesna); however, the largest effect on blood loss during myomectomy was recorded by the study that combined the occlusion of the uterine arteries and ovarian arteries using tourniquets prior to myoma enucleation. The uterus receives blood supply primarily from the uterine artery and secondarily from the ovarian artery [11–15]. Misoprostol, a prostaglandin E_2 analogue, was equally shown to significantly reduce blood loss, probably by causing uterine contraction and reducing uterine blood flow [16].

Other interventions have not been able to demonstrate the expected effect on blood loss that was theoretically postulated. The trial on oxytocin, a known uterotonic agent, showed no evidence of an effect on blood loss during myomectomy. This is consistent with other evidence that the myometrial concentration of oxytocin receptors is very low in nonpregnant uteri [17].

The use of 800 μg of misoprostol per rectally has been extensively studied in the obstetric patients and no serious side effects have been reported. Similarly, in our study, no serious side effects were observed. Only 2% of the patients complained of lower abdominal pain, which can be attributed to the strong uterine contraction. Minor side effects including pyrexia, shivering, nausea, and headache have been reported in obstetric practice because of centrally mediated prostaglandin E_1 effects [18] and shivering frequently following normal delivery; perhaps misoprostol administration increases its incidence by lowering the threshold for physiological shivering [19].

In a comparative study of r rectal versus oral administration of misoprostol, it was found that the longer half of rectally administered misoprostol could prolong uterine contraction compared to oral administration. Shivering and pyrexia were both found to occur less often in the rectal group. This effect could be caused by the lower peak serum concentration and longer half-life of rectal misoprostol compared to oral administration [19,20]. This was the basis of our choice of the rectal route of administration of misoprostol.

Misoprostol remains a very good option for reducing blood flow in procedures such as hysteroscopic and laparoscopic myomectomy whereby mechanical methods of reducing blood flow cannot be applied [21,22].

The CDMRS in patients prior to and after insertion of 800 μg of misoprostal rectally showed significant reduction in the blood flow of the segmental branch of the uterine artery and those supplying fibroids. The change in Doppler was seen either by elevated indices or no flow. Reduction in the volume of the fibroid was also noted.

The reduction of flow and decrease in size may be caused by the combined effect of myometrial contraction and vasoconstrictive effect.

Almost all of the patients in our study showed a response to misoprostol, where 50% of patients responded to misoprostol within 20 minutes and 90% responded within 40 minutes, which correlates with the peak serum concentration of misoprostol following rectal administration [19].

It is also suggested that we need at least 40 minutes to evaluate the maximum response to misoprostol in order to complete the study.

A few patients, who did not respond to misoprostol as observed by CDMRS, should be subjected to other means of mechanical or chemical interventions depending on the choice of the surgeon to reduce intraoperative blood loss.

Table 1 Volume of fibroids (comparison within groups).

Volume of fibroids	Mean ± SD	Mean difference	95% CI	*p*
Group A				
Baseline volume	423.4 ± 287.9			
At 20 min	383.1 ± 264.4	t_{0-20} = 40.3 cm^3	30.6–49.9 cm^3	0.00
At 40 min	346.9 ± 254.4	t_{20-40} = 36.2 cm^3	30.7–41.6 cm^3	0.00
Group B				
Baseline volume	410.8 ± 272.5			
At 20 min	410.6 ± 272.5	t_{0-20} = 0.2 cm^3	−1.69–0.99	0.08
At 40 min	417.3 ± 272.5	t_{20-40} = 6.7 cm^3	−14.64–3.28	0.21

CI = confidence interval; SD = standard deviation.

Table 2 Resistance index (comparison within groups).

Resistance index	Mean ± SD	Mean difference	95% CI	*p*
Group A				
Baseline RI	0.61 ± 0.15			
At 20 min	0.87 ± 0.16	t_{0-20} = 0.26	0.16—0.38 cm^3	0.00
At 40 min	0.95 ± 0.11	t_{20-40} = 0.08	0.33—0.04 cm^3	0.00
Group B				
Baseline RI	0.60 ± 0.17			
At 20 min	0.61 ± 0.17	t_{0-20} = 0.01	−0.004—0.001	0.267
At 40 min	0.60 ± 0.17	t_{20-40} = 0.00	−0.005—0.008	0.584

CI = confidence interval; RI = resistance index; SD = standard deviation.

The reduction in the blood flow on CDMRS was based on elevated indices, i.e., Pulstility Index (PI), RI, or no flow on color Doppler.

All of the patients were asked to follow up after surgery; however, because of the inconsistent timing of the surgeries, we received feedback on more than 20 patients and their gynecologists gave a positive response. Our study was limited to preoperative evaluation, therefore, this study can be an initiative for the gynecologists to do a postoperative study.

In conclusion, we firmly believe CDMRS may become an important tool for preoperative risk assessment of myomas for gynecologists planning myomectomy to use misoprostol preoperatively and in so doing reduce the likelihood of hemorrhage during surgery. We suggest that more randomized studies be conducted to validate our findings.

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