Uterine Artery Embolisation for Symptomatic Fibroids in a Tertiary Hospital in Singapore

Introduction

The standard therapy for fibroids has been surgical removal by hysterectomy or myomectomy if medical therapy fails. In 1995, Ravina et al. first reported the use of transcatheter uterine artery embolisation (UAE) as the primary treatment of fibroids with encouraging results. Following that, other centres have reported favourable clinical outcomes with UAE and this therapy is gaining popularity worldwide.

UAE is not a new vascular intervention technique as radiologists have been performing it for the management of acute obstetric and gynaecological haemorrhage for some time. The utilisation of UAE for the primary treatment of fibroids is, however, a more recent phenomenon. We report our preliminary experience with UAE in the local population.

Materials and Methods

All patients were referred by their attending gynaecologists for treatment of symptomatic fibroids, having declined, or deemed medically unfit for, surgery. Their symptoms were assessed to be attributable to fibroids and were of sufficient severity to be offered surgical management. The patients...
were treated according to a protocol approved by our institution’s ethics committee and with informed consent obtained from the patients. The inclusion criteria included healthy pre-menopausal women between 35 and 55 years of age not desirous of pregnancy, with large uteri (>12 weeks’ size) attributed to fibroids, and with at least 1 of the following symptoms: anaemia, menorrhagia, dysmenorrhea or pressure symptoms. Underlying gynaecological malignancy had to be excluded. The exclusion criteria included contraindications to contrast angiography, undiagnosed vaginal bleeding, patients on anticoagulants or having clotting disorders, and immunocompromised patients.

Each patient’s symptoms (menorrhagia, dysmenorrhoea and pressure symptoms) were graded on a 6-point scale from 0 (not present) to 5 (very severe). Current and previous medical therapy for fibroids was recorded. An ultrasound of the pelvis was also performed and the uterine volume and the largest diameter of the dominant fibroid was obtained. Pre-procedural blood tests included full blood count, coagulation profile and creatinine and electrolyte levels. Serum gonadotrophins (FSH/LH) were also obtained. The patient was also referred to the institution’s Acute Pain Service for evaluation by an anaesthetist and instructed on the use of patient-controlled analgesia (PCA).

The procedure was performed during the first 10 days of the patient’s menstrual cycle and a urine pregnancy test was administered when necessary. The patient was admitted a day prior to the procedure and was required to fast for 6 hours before the procedure. Prophylactic intravenous antibiotic ceftriaxone sodium 2 g (Rocephin, Roche Pharmaceuticals, New Jersey, USA) was administered an hour before the procedure. Intra-procedural sedation and analgesia was administered by the attending radiologist utilising midazolam hydrochloride and fentanyl citrate. The right common femoral arterial approach was utilised; a flush aortogram was first performed with the catheter tip positioned at the level of the renal arteries to identify the uterine arteries and any collateral supply from the ovarian arteries (Fig. 1). After catheterisation of the internal iliac arteries with 4 to 5F visceral catheters (Cobra or Sidewinder; Terumo, Tokyo, Japan), sub-selective catheterisation of the uterine arteries were performed with 3F micro-catheters (Tracker 325, Target; Boston Scientific, USA) (Fig. 2). Both uterine arteries were embolised with polyvinyl alcohol (PVA) particles of 355 to 500 microns (Contour, Target; Boston Scientific, Massachusetts, USA) (Fig. 3). All patients were admitted for at least 24 hours after the procedure for pain control. After embolisation, morphine and an anti-emetic agent, ondansetron hydrochloride (Zofran; GlaxoSmith Kline, Uxbridge, Middlesex, UK), were administered via a PCA for pain relief. The PCA was set at morphine 1 mg/bolus with a 5-minute lockout at a maximum of 10 mg/h. Non-steroidal anti-inflammatory drugs (NSAIDs) [Naproxen 550 mg bd (Synflex, Roche, Hertfordshire, UK)] were administered routinely to the patients for a week. The amount of morphine required, length of hospital stay and occurrence of any complication was noted.

After discharge from the hospital, the patients were reviewed at 2, 6, 12 and 24 weeks and subsequently, at 6-monthly intervals. The severity of the presenting
symptoms was reassessed on the same 6-point scale. Haemoglobin level test and pelvic ultrasonography were performed at 12 and 24 weeks after the procedure and subsequently, at 6-monthly intervals. In addition, the patient was asked to rate her satisfaction level on a 5-point scale of very satisfied/moderately satisfied/no opinion/moderately dissatisfied/very dissatisfied.

The statistical comparison of symptom scores before and after embolisation was done by means of non-parametric tests and the Wilcoxon matched pairs signed ranks test. All statistical tests were interpreted at the 5% significance level (two-tailed). All numerical results were expressed as mean and range.

Results

Twenty women aged between 38 and 52 years (mean, 43) were referred for UAE for the treatment of symptomatic fibroids. Menorrhagia was present in 17 women, dysmenorrhoea in 10 women, pressure symptoms in 11 women and anaemia in 16 women. The mean haemoglobin level was 9.9 mg/dL. The subjects had previously received medical treatment, namely, hormonal therapy [combination of progestogen and/or gonadotropin-releasing hormone (GnRH) agonists], NSAIDs and anti-fibrinolytic agent. Two patients had undergone a previous myomectomy. The mean volume of the uterus was 308 mL (range, 158 to 1003) and the mean diameter of the largest fibroid was 6.2 cm (range, 3.1 to 13.3).

UAE was successfully performed on all patients. Nineteen patients had both uterine arteries embolised; 1 patient had only the right uterine artery embolised on account of hypoplasia of the left uterine artery. The mean procedure time was 120 min (range, 40 to 300). There were no complications associated with the use of contrast mediums or catheters. Two patients had small groin haematoma at the femoral arterial puncture site that resolved uneventfully. Post-procedural pain was well-controlled in 14 women. Three women had severe post-procedural pain despite the administration of morphine through the PCA. The pain improved a few days later with continued analgesia. Fever was encountered in 3 women (2 of whom also had severe pain) that resolved with medical therapy. The mean morphine usage for pain control was 24 mg (range, 7 to 57) and the mean hospital stay was 3.5 days (range, 2 to 9).

The mean follow-up was 56 weeks (range, 6 to 168). All patients reported improvement in the presenting symptoms. Objective improvement, in terms of reduction of uterine and fibroid sizes, was determined by ultrasonography. The mean decrease in uterine volume at 6 months after embolisation was 145 mL (range, -125 to 421; n = 17) and at 24 months after embolisation, 193 mL (range, 124 to 481; n = 6).

The mean decrease in diameter of the dominant fibroid at 6 months was 1.5 cm (range, -4.2 to 6.2; n = 17) and at 24 months post-embolisation, 2.8 cm (range, -0.8 to 5.5, n = 6). The mean haemoglobin level prior to procedure was 9.9 g/dL (range, 6.1 to 14.5); the mean post-procedural haemoglobin level was 12.7 g/dL (range, 8.7 to 14.6). The mean improvement in haemoglobin level was 3 g/dL (range, -3.3 to 8.1).

Overall, 10 patients were very satisfied, 7 were moderately satisfied and 3 did not express an opinion on the results of the procedure. At the time of reporting, it was <15 weeks post-procedure for all the patients.

One patient required re-embolisation 6 months after the initial procedure. There was an initial reduction in uterine and dominant fibroid size of 36% and 4%, respectively, at 3 months post-embolisation. This, however, was superseded by an increase in the size of the dominant fibroid and the patient having anaemia from menorrhagia, highlighted at the 6-month review. Following re-embolisation of the left uterine and left ovarian artery, the menorrhagia resolved completely and there was improvement in the serum haemoglobin level.

In a second patient, there was complete resolution of both dysmenorrhoea and menorrhagia at 6 months’ follow-up, with concomitant changes in serum haemoglobin level (7.8 to 12.2 g/dL) and uterine and dominant fibroid sizes. This patient later presented to the attending gynaecologist with recurrent symptoms of menorrhagia. Unfortunately, she was lost to follow-up.

Two women, aged 49 and 52 years, experienced transient amenorrhoea at 12 and 24 weeks, respectively, after UAE. The other women did not have symptoms associated with menopause.

Discussion

The standard management for fibroids is surgery, either by hysterectomy or myomectomy. For women with multiple or large fibroids, myomectomy can be complicated by severe intraoperative bleeding. Hysterectomy is associated with increased morbidity. Medical therapy (progestosterone, GnRH agonists) is effective, but is associated with recurrence after cessation of treatment. Moreover, a limit of 6 months is imposed on GnRH agonists due to bone loss. Since the first report of UAE as the primary treatment for uterine fibroids, the procedure has grown rapidly in popularity with subsequent reports showing encouraging results.\[^{1-9}\]

The biology of fibroids following UAE is largely unknown. Ravina et al believed that UAE reduced the blood supply to the fibroid, not amounting to massive necrosis of the tumour. Indeed, the description by Siskin et
of a hysterectomy specimen showing hyaline degeneration in a fibroid following UAE (with PVA particles of 500 to 710 microns) appears to substantiate this theory. However, other investigators reported fibroid infarction in hysterectomy specimens that occurred with PVA particles of various sizes. A recent review of the literature compared the results of 17 current reports on UAE with established data of surgery. The review showed that the mortality rates of UAE and hysterectomy were low, at 0.01% for both. The operative injury of surgery (myomectomy and hysterectomy both at 1%) was, however, higher than that for UAE (0%). The recurrence rate of fibroids following UAE (20%) was higher than that of myomectomy (10%), as was the re-operation rate (5% for UAE and 1% for myomectomy). UAE recorded 90% improvement in menorrhagia while myomectomy recorded 81% improvement. The risk of premature menopause is unique to UAE, which is estimated to be 5%.

Of the 19 women still on follow-up, all 17 who initially had menorrhagia reported improvements in their symptoms, and all women who initially reported dysmenorrhoea and pressure symptoms reported improvement.

The mean score for all 3 categories showed improvement. For patients who presented with menorrhagia, the mean score dropped from 4 (range, 1 to 5) to 0 (range, 0 to 5) \( (P < 0.001) \). The mean score for dysmenorrhoea dropped from 3.7 (range, 1 to 5) to 0 (range, 0 to 3) \( (P < 0.003) \). The mean score for pressure symptoms dropped from 3.5 (range, 1 to 5) to 0 (range, 0 to 2) \( (P < 0.005) \). Improvement was seen in the rise of the mean serum haemoglobin level from 9.9 g/dL (range, 6.1 to 14.5) to 12.7 g/dL (range, 8.7 to 14.6) \( (P < 0.001) \). This may be partly due to the supplementary iron therapy that the patients were on.

When compared to another Asian series, at the 6-month follow-up, there was a reduction in the dimensions of the dominant fibroid, albeit to a lesser degree (50.3% compared to 24%). In our series, with the benefit of a longer period of follow-up, this decrease was sustained at 2 years and reached 43%.

Smith et al attributed treatment failure after UAE for fibroids to coexistent adenomyosis. It is difficult to distinguish adenomyosis from uterine fibroids and transabdominal ultrasonography lacks the specificity required to differentiate the former from the latter. We did not use magnetic resonance imaging (MRI) to document the presence of adenomyosis, though it has a reported sensitivity of 0.7 and specificity of 0.86. Equivocal data have been published on the clinical usefulness of UAE in coexisting adenomyosis while treating fibroids. Additional blood supply from ovarian arteries has been postulated to be the cause of UAE failure and supplementary ovarian artery embolisation has been attempted. To this measure, 1 of the 2 cases of recurrence was successfully treated with ovarian and uterine artery embolisation.

We recruited only women not desirous of future pregnancies as the effect of UAE on ovaries (non-target embolisation), the myometrium and the endometrium are unknown, similar to the practice in other studies. However, amenorrhoea following UAE is indicative of ovarian failure. Flow to ovarian arteries has been shown to decrease by colour Doppler analysis, though there is no direct correlation with the eventual development of amenorrhoea. Indirect assessment of ovarian function post-UAE by FSH level measurements showed no significant difference in the onset of menopausal symptoms amongst younger women (<45 years) and women >45 years old. Other reports document ovarian failure in women >45 years old post-UAE. In addition, there have been reports of ovarian failure occurring in women <45 years, as well as in procedures which utilised bigger PVA particle sizes ranging from 500 to 700 microns.

Two women in our study, aged 49 and 52 years, were amenorrhoeic at 12 and 24 weeks, respectively, after the procedure. With further follow-up, normal menstrual cycle resumed and the elevated FSH levels returned to normal, confirming that both were cases of transient ovarian failure similar to the report by Amato and Roberts. Though UAE can result in amenorrhoea, especially in peri-menopausal women, successful pregnancies have been reported elsewhere, with an incidence as high as 27%. The risk of premature menopause is estimated to be about 5%. Further studies are needed regarding the effect of UAE on ovarian function and pregnancy, as well as PVA particle size as a possible confounding factor.

During UAE, the pelvic organs are under direct irradiation and the resulting radiation dose is a cause of concern to many women. Published data have shown remarkable decrease in radiation dosages for UAE, after the implementation of measures such as the use of low-frequency pulsed fluoroscopy (15/s), bilateral femoral puncture with simultaneous embolisation of the uterine arteries, as well as limited oblique and magnified fluoroscopy. There were significant reductions in both the estimated absorbed ovarian dose and the absorbed skin dose. In our study, 3 interventional radiologists with a high level of radiation awareness performed all the embolisations. In the early report by Goodwin et al, one subject developed pyometra, thereby requiring hysterectomy. Subsequently, they administered antibiotics to all women. This became standard practice in subsequent reports. Awareness of potential infection is paramount, as a necrotic fibroid is a conducive environment for the propagation of infection. There has been a fatality involving a 51-year-old woman.
Three days after UAE, a urinary tract infection was treated with cephalexin and the patient was discharged the following day, only to return 7 days later with Escherichia coli septicemia and disseminated intravascular coagulation. Surgery revealed a large, infected necrotic fibroid, and death occurred 15 days later.\(^8\) There was another unreported death in Italy where massive pulmonary embolism occurred 24 hours after an uneventful UAE. The autopsy revealed that it originated from a pelvic vein thrombosis.\(^28\) In the early series of 11 patients by Goodwin et al.,\(^4\) a woman developed pyometra 3 weeks after UAE despite pre-procedural antibiotics (second-generation cephalosporin). A hysterectomy was performed and she was well at her last follow-up.

Infection can be difficult to differentiate from the fever of post-embolisation syndrome. Three (38%) patients in Bradley’s series developed fever (more than 37.5°C) that was attributed to post-embolisation syndrome and it resolved without antibiotic therapy.\(^8\) Despite this, there has to be a heightened awareness of the possible complication of infection in the post-procedural period and the patient should be made fully aware of the necessity for prompt medical attention. The literature reveals an overall peri-procedural complication rate of 8.5%; serious complications were seen in 1.25%.\(^29\) With strict adherence to protocol and education of our patients, we did not encounter a severe infection. In 3 of our patients with prolonged fever, oral antibiotic therapy was instituted and this was successful in preventing an infection. We have not encountered any catheter complication. Intimal dissections\(^2,3,6,7\) and small arterial perforations\(^3,7\) have been reported, but they were uneventfully managed with coil embolisation.

There are several limitations in this study. The number of patients in this study is small partly because of the need to adhere strictly to protocol with regard to indications and to limit our referrals to only those from gynaecologists. We felt that this strategy was important in giving wider acceptance of this procedure locally. As ultrasonography is used to assess size, there is a likelihood of variation due to inter-operator differences. The examination was also not timed at the same period within the menstrual cycle, which may have added to minor discrepancies in measurements. MRI could be a more objective method of assessment, but we decided to utilise only ultrasonography in view of the significantly higher cost of MRI.

A 10-member multi-disciplinary expert panel conference was convened in the United States on UAE recently and their conclusion was that high-quality data are needed to convince gynaecologists of the benefits of UAE for the primary treatment of fibroids.\(^11\) They proposed a randomised control trial between UAE and surgical management (hysterectomy and myomectomy) with follow-up periods of 3 to 5 years. An alternative proposal was the establishment of a registry of UAE in the primary treatment of fibroids. The controls would consist of women with untreated fibroids and those treated with methods other than UAE. It may be timely to establish a registry of UAE in the primary treatment of fibroids in Singapore. As this technique is in its relative infancy in Singapore, one could potentially obtain quality data to further refine the technique of UAE in the primary treatment of fibroids and gain greater acceptance of UAE in the medical community.

**Conclusions**

The mid-term results of UAE for the treatment of symptomatic fibroids in our hospital indicate this to be a safe and effective therapeutic option. A longer period of follow-up with a greater number of patients in this ongoing study will be needed to confirm that UAE is a viable option, acceptable to both patients and clinicians.

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**REFERENCES**

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