

Comparison of particle penetration with non-spherical polyvinyl alcohol versus trisacryl gelatin microspheres in women undergoing premyomectomy uterine artery embolization

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KEYWORDS

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AIM: The purpose of this study was to compare the depth of vascular penetration of non-spherical polyvinyl alcohol (PVA) versus trisacryl gelatin microspheres (MS) in women undergoing uterine artery embolization (UAE) immediately before transabdominal myomectomy.

MATERIALS AND METHODS: A total of 17 patients who had been referred for embolization before myomectomy underwent bilateral uterine artery embolization using either 355-500 μm PVA (group A) or 700-900 μm MS (group B). The depth of penetration of the particles was assessed by identifying their presence and location in the resected specimen.

RESULTS: Of the 17 women enrolled in this study, 10 were in group A and 6 in group B. One woman underwent embolization using both types of particle and was excluded from the analysis. Embolic particles were significantly ($p=0.048$) more frequently located within the fibroid (4/6, 67%) in Group B than Group A (1/10, 10%). Particles were also identified in the perifibroid tissues in 4/6 (67%) in Group B and 4/10 (40%) in Group A, with no statistical difference. There were no procedural complications.

CONCLUSION: MS particles (700-900 μm) penetrate significantly deeper into leiomyomata compared with non-spherical PVA (355-500 μm). MS may therefore confer advantages in UAE, as they may more specifically target the fibroid, allowing an earlier end-point to embolization and minimizing ischaemic damage to normal myometrium and ovaries.

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Introduction

Uterine leiomyomas are the commonest pelvic tumors in women. Conservative treatment with hormonal manipulation has no permanent effect

and hysterectomy is the current main treatment for women with symptomatic fibroids. Since the first report of successful uterine artery embolization (UAE) to treat symptomatic fibroids, the efficacy of UAE has been widely reported, with improvement in menorrhagia and pelvic pain in approximately 80% of women and also significant fibroid and uterine shrinkage.¹⁻⁶

UAE is associated with a low rate of significant complications. Uterine necrosis has been reported

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in less than 1% of procedures.⁷ Infection is one of the most serious complications and may lead to hysterectomy^{4,8-10} in 1-2% of procedures. Transient or permanent amenorrhoea occurs in up to 14% of procedures¹¹ but appears to be related to age, women closer to the menopause being at greater risk.¹¹ Some of these complications may be due to non-targeted devascularization of the uterus and ovaries when anastomotic vessels are embolized. An ideal embolic particle would therefore embolize fibroids but allow continued patency of the main uterine arteries to perfuse normal myometrium and ovaries.

There are three main types of particulate embolic agents currently being used in UAE for fibroids: non-spherical polyvinyl alcohol (PVA), gelatin sponge and trisacryl gelatin calibrated microspheres (MS). PVA is the most commonly reported embolic agent.^{2,7,8,12} Because of the irregular shape and size of these particles and their tendency to aggregate, occlusion tends to be more proximal than required.¹³ Gelatin sponge is a temporary agent, which should allow recanalization of the uterine artery once the fibroid has infarcted. It has been shown to be successful clinically, and theoretically may better preserve fertility and the ability of the uterus to maintain a full-term gestation after embolization.^{14,15} MS have been used extensively in the field of neuroradiology where precise calibration of the particles is advantageous.¹⁶⁻¹⁸ This advantage has prompted investigators to turn to MS as an alternative to PVA particles for UAE, in the hope that fibroid embolization will occur while patency of myometrial branches of the uterine artery is maintained. The end-point of embolization with MS is therefore, a "pruned tree" appearance of the uterine artery, with preservation of antegrade flow, as opposed to a standing column of contrast medium due to complete cessation of flow, which is the angiographic end-point with PVA and gelatin sponge. Early experience with MS indicates that this technique is safe and efficacious for the treatment of uterine leiomyomas,^{19,20} and animal experiments have shown a significant reduction in ischaemic injury to the uterus compared with the PVA technique.²¹

In our institution, gynaecologists occasionally request uterine artery embolization before myomectomy in situations where excessive blood loss is anticipated. These include women with previous myomectomy, those with massive fibroids extending beyond the level of the umbilicus, or Jehovah's Witnesses who would not consent to blood transfusion. PVA or MS are routinely used in these embolizations and all specimens are sent for

histologic analysis. This offers the opportunity to analyze the distribution of the different particulate agents within the fibroid and perifibroid tissues.

Materials and methods

This was a prospective study. Approval by the local research and ethics committee was not required. Seventeen women who were scheduled for premyomectomy uterine artery embolization were informed about the benefits and potential risks of the procedure and written informed consent was obtained from each individual. All women had been offered open surgical removal of their fibroids by myomectomy, but had been advised to undergo premyomectomy UAE to minimize hemorrhage. The embolization was usually carried out on the morning of surgery but occasionally in the afternoon before surgery next morning.

Pre-embolization imaging

Before surgery all women had transabdominal or transvaginal ultrasound studies of the pelvis to determine the location, number and size of leiomyomas and to exclude alternative disease.

Procedure

A standard unilateral transfemoral approach under local anesthesia was preferred in all cases, with selective catheterization of both uterine arteries using five French catheters. The women were divided into two groups denoting the embolic agent involved: PVA, granulometric range 355-500 μm (Contour, Target Vascular, Boston Scientific, Cork, Eire), was used in group A, and MS, range 700-900 μm (Embosphere, Biosphere Medical, Roissy, France), in group B. The selection of embolic agent was based on its availability and the personal preference of the operator.

Angiographic end-point of embolization

Embolization was performed in free flow, with the catheter tip placed 2-4 cm distally into the uterine artery. Each vial of PVA and MS was diluted in 20 ml of iodinated contrast medium (Niopam 200, Bracco, Bucks, UK). Before each injection, the mixture was agitated to maintain homogeneous particle suspension. Injection of the mixture was performed slowly with fluoroscopic control by using 2 ml syringes. In group A, embolization was stopped when contrast stasis was observed in the proximal part of the

uterine artery. In group B, embolization was stopped when a “pruned tree” appearance with continued antegrade flow was achieved. Gelatin sponge was then used as a secondary embolic agent to achieve stasis in the proximal part of the uterine artery, to ensure minimal blood loss during surgery.

Postembolization myomectomy

After embolization, all the women underwent transabdominal myomectomy either on the same day as UAE or the next morning. The surgeon was not aware of the embolization agent used for each case. At surgery, excision of all visible uterine leiomyomas was completed.

Histopathologic study

Specimens were fixed by immersion in 4% buffered formalin. When practical, all available tissue underwent histopathologic examination; in the largest tumors, representative tumor blocks from the centre of the tumor and the periphery were selected. After fixation, specimens were embedded in paraffin. Sections were prepared for histologic examination with hematoxylin and eosin stain. Histopathologic analysis was performed by the same pathologist (MW). The particle distribution was classified as (a) within the leiomyomatous tissue, (b) in perifibroid tissue or (c) not visualized in the analyzed specimens.

Results

Patient demographic data are shown in Table 1. The mean age of the women was 39.5 years (range, 33–49 years). All women included in the study were premenopausal and 71% presented with heavy menstrual bleeding, 24% with dysmenorrhoea and 47% with pelvic pressure.

Embolization was successfully completed in all cases except 1 in which the right uterine artery could not be selectively catheterized. In group A, 10 women were treated with 355–500 μm PVA. In group B, 6 women were treated with 700–900 μm MS, with gelatin sponge as secondary embolic agent. PVA was used as secondary embolic agent in 1 case because there was insufficient stock of MS available to complete the embolization procedure for the second uterine artery. This case was excluded from the statistical analysis.

There was no significant difference in age between the two groups ($p=0.357$, Student's *t*-test). The median period between embolization and

surgery was 6 h in both groups (range, 5–18 h). Median tumor weight was 962 g in group A and 1410 g in group B. This difference was not statistically significant ($p>0.05$, Mann-Whitney test) but this may be a reflection of the small sample size. There was no significant intraoperative complication or complications related to UAE. Because in 1 case it was not possible to resect the fibroids while preserving uterine integrity, the patient proceeded to hysterectomy.

Histologically, non-refractile foreign material within blood vessels either within the fibroid or in the perifibroid tissues could be detected in 10 cases (59%). Under microscopy, PVA particles appear as aggregates of irregularly shaped non-refractile material (Fig. 1). MS appear as isolated or clusters of spherical material with occasional slight deformity (Fig. 2). In group A, intravascular PVA particles were detected in 5 cases (50%), but only 1 of these (10%) had PVA particles within the fibroid arteries. In group B, MS were detected in 4 cases (67%), within the fibroid arteries in all of these. The woman treated with both embolic agents had MS detected in the fibroid and PVA in the perifibroid arteries, but this case was excluded from the statistical analysis. MS were located significantly more frequently in tumor vessels, whereas PVA particles were found predominantly in the perifibroid tissues ($p=0.048$, Fisher's exact test).

Discussion

UAE is emerging as an effective, non-surgical treatment for women with symptomatic uterine fibroids.

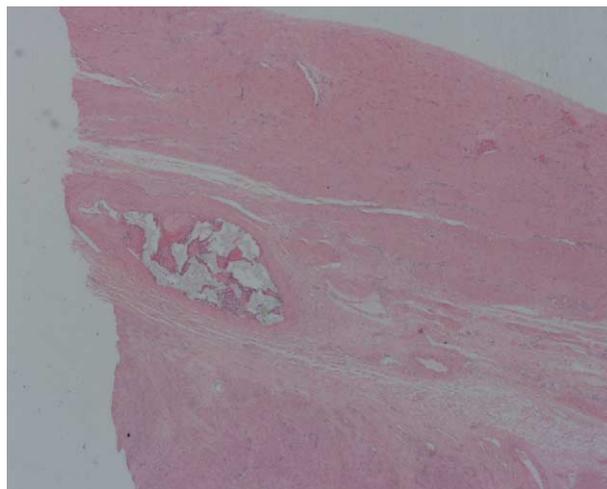


Figure 1 Photomicrograph of perifibroid tissue. Small fragments of polyvinyl alcohol particles were identified in an artery within the perifibroid myometrium (hematoxylin and eosin stain; low magnification).

Table 1 Patient demographics and results of UAE and myomectomy

Case	Age	Presenting complaint	Embolic agent	Particles observed
1	34	Menorrhagia	PVA 355-500 μm	Perifibroid + myometrium
2	37	Dysmenorrhoea, menorrhagia	PVA 355-500 μm	No
3	38	Pressure symptoms, menorrhagia	PVA 355-500 μm	Outside fibroid
4	43	Pressure symptoms	PVA 355-500 μm	No
5	46	Menorrhagia, dysmenorrhoea	PVA 355-500 μm	No
6	44	Pressure symptoms, dysmenorrhoea	PVA 355-500 μm	Perifibroid; 1 particle in fibroid
7	39	Menorrhagia, pressure symptoms	PVA 355-500 μm	No
8	42	Pressure symptoms	PVA 355-500 μm	No
9	34	Pressure symptoms	PVA 355-500 μm	Perifibroid + myometrium
10	44	Pressure symptoms	PVA 355-500 μm	Perifibroid + myometrium
11	33	Menorrhagia	MS 500-900 μm ; PVA 355-500 μm	PVA outside fibroid; MS in fibroid
12	45	Dysmenorrhoea, menorrhagia	MS 700-900 μm ; gelfoam	No
13	39	Menorrhagia	MS 700-900 μm ; gelfoam	MS in fibroid
14	49	Pressure symptoms, menorrhagia	MS 700-900 μm ; gelfoam	MS in fibroid; gelfoam at periphery
15	33	Menorrhagia	MS 700-900 μm ; gelfoam	MS in fibroid
16	38	Menorrhagia	MS 700-900 μm ; gelfoam	No
17	34	Menorrhagia	MS 700-900 μm ; gelfoam	MS in fibroid

Age, years; PVA, non-spherical polyvinyl alcohol particles; MS, trisacryl gelatine calibrated microspheres.

The procedure was first tried in 1994, when it was used as an adjunct to operative treatment of fibroids.²² Fibroids derive their blood supply predominantly from the uterine arteries, and the aim of the procedure is to occlude both uterine arteries and cause ischaemia and shrinkage of the fibroid. The normal myometrium and endometrium are inevitably subjected to a certain degree of ischaemic insult, depending on the type and size of the embolic particles used.²¹ The pain experienced after UAE is related to myometrial ischaemia.²³

Complications such as uterine necrosis or infection leading to emergency hysterectomy and ovarian failure have been related to over-embolization.^{2-4,24} Matson et al.²⁵ and Wolanske et al.²⁶ have also reported reflux and reversal of flow in the

ovarian arteries during UAE, confirming the risk of non-targeted ovarian embolization in UAE. Ideally, embolization should cause fibroid necrosis without effect on the normal myometrium and ovaries, but in practice this cannot be achieved since it is not possible to perform selective embolization of every fibroid. A more practical approach to this procedure is to use the difference in vascularity and in sensitivity to ischaemia between fibroids and normal myometrium and endometrium. Fibroids are more vascular than the surrounding myometrium and endometrium, and there is predominant blood flow to the fibroid at the beginning of embolization. In addition, because fibroids are metabolically active growing tumors, they are more sensitive to ischaemia than the normal

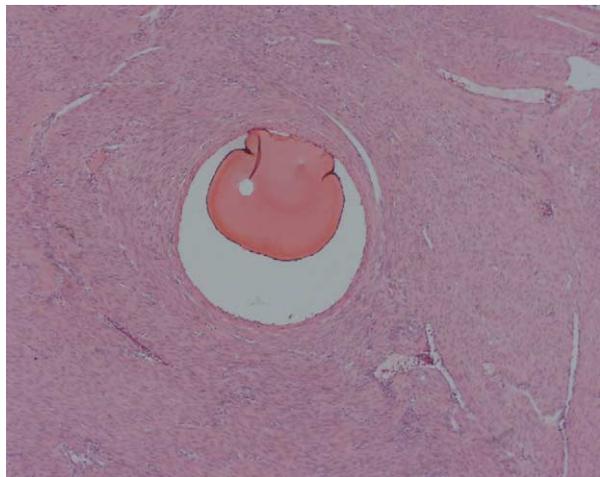


Figure 2 Histologic section (hematoxylin and eosin stain; high magnification) of leiomyoma, showing a microsphere particle within an artery in the leiomyoma.

myometrium and endometrium. Hence, some investigators have applied these facts to define the end-point of embolization by (a) the disappearance of hypervascularity of the fibroids, (b) reduction of the distal flow of the uterine artery and (c) patency of the main uterine artery, including cervicovaginal branches, at the end of embolization.^{20,27}

The choice of embolic agent plays an important role in determining the extent of arterial occlusion achieved during embolization. For several years, PVA have been used in UAE. However, there are data suggesting that PVA may have some undesirable characteristics. Despite recent improvement in calibration, the irregular shape of PVA particles is associated with a large granulometric size range.^{28,29} Therefore, there is a risk of injecting particles smaller than the desired size as well as aggregation of particles. As a result, the behaviour of PVA during embolization is unpredictable, and the level of arterial occlusion does not correlate with the size of the PVA particles.²¹ Gelatin sponge alone has also been used for embolization of fibroids, although the reported experience is very limited.¹⁴ Because of the perception of gelatin sponge as a temporary agent, it has been suggested for women who may want to preserve their fertility.

MS have featured in the field of neuroradiology for several years. Experimental studies have demonstrated that spherical embolic particles are more effective than other particles in achieving targeted vascular occlusion and tissue necrosis.³⁰ Published reports have shown UAE using MS has encouraging results for treatment of uterine leiomyomas.^{19,20} Pelage et al.²¹ used various sizes of MS

and PVA to embolize uterine arteries of sheep. A significant difference was detected between PVA and MS in the degree of uterine injury, with greater ischaemic injury in the case of PVA regardless of size of treated uterus. On the other hand, the extent of uterine necrosis with calibrated MS did correlate with size.

This small study confirms the findings in animal studies that MS are more likely to penetrate the fibroid vasculature than PVA. The likely explanation is that the PVA particles tend to aggregate, which obstructs the vascular bed at a more proximal level. Despite this fact, there is no published evidence of improved efficacy of MS over PVA. A possible explanation is that even though PVA particles tend to aggregate before reaching the inner fibroid vasculature, they have a profound effect on the perfusion of the uterus, leading to global ischaemia. This in turn induces fibroid infarction without actually occluding the inner fibroid vessels. PVA particles smaller than 300 μm may penetrate further into the tumoural vessels but are associated with an increased risk of ovarian and uterine ischaemia from non-targeted embolization.³¹ It has been reported that the diameter of the utero-ovarian anastomoses in women with fibroids is less than 500 μm and therefore MS should be at least this size or larger.³² A case report³³ of fatal sepsis after UAE with 500-700 μm MS has been described and it is our practice to use 700-900 μm particles. MS of size 700-900 μm may be associated with less uterine ischaemic injury compared with PVA of size 355-500 μm , but this is yet to be confirmed by large studies. This size range may be presumed effective in tumor devascularization, as the particles were found within the leiomyomas in this study. However, these presumptions need to be substantiated by larger study series.

Histologically, we were able to identify embolic particles in only 59% of all specimens. The failure to identify embolic particles in 41% of specimens may be due to the fact that the particles were within the perifibroid arterial plexus in the surrounding normal myometrium, not excised with the leiomyomas. We were not able to demonstrate any relationship between the quantity of embolic material injected and the ability to detect the particles in the resected specimen, as this was not recorded in all cases. Nor were we able to determine whether the size of the fibroids or their vessels made any difference to the detection of particles in the resected specimens. In addition, sampling error could have been present when representative tumor blocks were selected for histopathologic study.

The main limitation of our study is its small

number of cases, and a larger series may be required to substantiate these findings. However, it might be difficult to obtain a large series because many women opt for a non-surgical solution, and the combined approach is reserved for women with very large fibroids wishing to preserve their uterus. Despite the small size of this study, we have shown a significantly more frequent intravascular penetration of the uterine fibroids with MS than with PVA, which supports the findings in animal studies. This would seem to support the claim that MS may be more effective than PVA in selectively devascularizing fibroids, but whether this translates into more effective clinical results with fewer complications is unknown. Larger studies comparing clinical outcomes between the two types of particle, especially complication rates, are now required.

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