**A retrospective cohort study comparing a novel, spherical and resorbable particle against 5 established embolic agents for Uterine Fibroid Embolization (UFE)**

**Keywords**

Fibroid, Uterus, Arteries, Interventional Radiology, Magnetic-resonance Imaging

**Abbreviations and Acronyms**

AF: All fibroid

ANOVA: Analysis of Variance

CI: Confidence interval

DF: Dominant Fibroid

MRA: Magnetic Resonance Angiogram

MRI: Magnetic Resonance Imaging

PVA: polyvinyl alcohol

RR: Relative risk

UFE: Uterine Fibroid Embolization

**Introduction**

Uterine Fibroid Embolisation (UFE) has several benefits over traditional surgical techniques in the management of symptomatic uterine fibroids, which makes it a favourable option for patients [(1)](https://paperpile.com/c/Yj4trw/4Q76S). Despite this, a small proportion of patients have symptom recurrence related to incomplete fibroid infarction demonstrated by post-procedural MRI [(2,3)](https://paperpile.com/c/Yj4trw/ezMTy%2B4xLvZ). To ensure optimal patient outcomes, any new embolic agent considered for use in UFE should therefore have proven MRI-determined infarct rates equivalent to current embolic agents prior to their widespread adoption. We therefore aimed to compare the percentage fibroid infarct of a new embolic agent (Gel-bead, Teleflex, previously marketed as Optisphere by Medtronic) against 5 other routinely used embolic agents in a cohort study to rigorously assess its suitability for fibroid embolization. This follows on from our recent prospective case series of Gel-bead (previously Optisphere)[(4)](https://paperpile.com/c/Yj4trw/p0Lp) in uterine fibroid embolization (UFE) which found promising results, but was not a comparative study.

**Gel-bead**

Gel-bead (Teleflex) is a bioresorbable gelatin embolic of calibrated spheres. It is available in several size ranges, similar to other calibrated particles. After use, Gel-bead resorbs by approximately 12 weeks [(5)](https://paperpile.com/c/Yj4trw/yxZUN).

Shared decision making and patient-directed care continues to play a larger role in what patients are offered by Healthcare providers [(6,7)](https://paperpile.com/c/Yj4trw/2ZWQI%2BVErDp). Considering industry and patient scrutiny is mounting over plastic medical materials[(8)](https://paperpile.com/c/Yj4trw/ApoW5), an embolic agent which resorbs fully after use could be potentially favorable to patients opting for fibroid embolization.

Potential advantages of Gel-bead over currently available but non-calibrated, resorbable gelatin slurry, such as Gelfoam (Pfizer), include more consistent embolic characteristics/ a more predictable clinical response [(9)](https://paperpile.com/c/Yj4trw/FxnCf), a potential lower infection risk [(9)](https://paperpile.com/c/Yj4trw/FxnCf), and higher uterine artery patency rates [(10)](https://paperpile.com/c/Yj4trw/JsolM) (which may have important implications for patients with fertility wishes[(11)](https://paperpile.com/c/Yj4trw/lcalF)).

## Materials and Methods

Ethical approval for this study was obtained from the Research Ethics Committee (Regional) with Regulatory approval from the Medical Device Authority (National). Adherence to the ethical principles of the Helsinki Declaration was maintained throughout the study.

A retrospective cohort study was performed through analysis of a prospectively collected database of patients undergoing fibroid embolization at a single centre UK University teaching Hospital collated from March 2006 to June 2018. All embolizations were performed by 3 experienced Interventional Radiologists throughout this period.

 **Sample size calculation**

A sample size of 20 consecutive patients in each arm (120 patients total) was selected based on a dichotomous (100%, <100% infarction) non-inferiority calculation (alpha 5%, Power 1-beta 90%, Percentage success rate 86%, non-inferiority limit 33%). Percentage success rate is the percentage of patients with complete dominant fibroid infarction. The non-inferiority limit was deemed a clinically important difference, taking into account results of a recent meta-analysis of dominant fibroid infarction (complete infarction in 33.3 to 92.3% patients).

Embolic agents (used concurrently) included in the study were:

* + Gel-bead (Teleflex)
	+ Embosphere® Microspheres (Merit Medical Systems)
	+ Contour™ PVA Embolization Particles (Boston Scientific)
	+ Embozene® Microspheres (CeloNova BioSciences)
	+ Bead-Block® (BTG)
	+ Gelfoam (Pfizer)

**Pre-embolization**

Inclusion criteria for the study were: female patients aged over 18 years practicing effective contraception with symptomatic fibroids requiring treatment. Exclusion criteria were hypersensitivity to porcine products or iodinated contrast agents, or inability to consent for the procedure or study. All patients underwent baseline MRI performed prior to embolization to confirm presence of viable fibroids without malignant features and to assess arterial anatomy, using a Siemens 1.5T Aera or 3T Skyra. Axial/ sagittal T2, fat-saturated T1 pre-contrast and post-contrast sequences with a volume MR contrast angiogram acquisition were performed.

**Embolization technique**

Embolization was performed in all patients through a unilateral ultrasound guided femoral approach. Most common catheters utilised were the 4 French (Fr/Ch) C2 or Rim catheters (Cordis Tempo) through a 4 Fr sheath, with the contralateral side treated first. A microcatheter was used in cases of significant arterial tortuosity (Progreat 2.7 Fr Terumo Corp). Embolization was performed to stasis in the distal uterine artery.

Consistent embolic particle sizes were used for each cohort. For Gel-bead (Teleflex), 700-1000 micron particles were used. For Embosphere Microspheres (Merit Medical Systems), 500-700 micron particles were used initially, followed by 700-900 micron and then 900-1200 micron particles. For Contour PVA Embolization Particles (Boston Scientific), 355-500 micron particles were used initially, followed by 500-710 micron particles. For Bead-Block (BTG), 700-900 micron particles were followed by 900-1200 micron particles. For Gelfoam (Pfizer), the foam sheets were cut into squares of <5mm and broken down into a slurry through repeated mixing by ‘pumping’ between two syringes and a three way connector[(12)](https://paperpile.com/c/Yj4trw/AKmnx).

Intra procedural conscious sedation was administered with intravenous Fentanyl/ Midazolam administered by a specialist nurse. Post-operative pain relief was maintained through use of a morphine Patient-Controlled Analgesia (PCA). Patients were admitted overnight for analgesia and discharged the next day.

**Follow-up protocol**

At 3 months, MRI/MRA was repeated with the same protocol as the pre-embolization MRI. This was reviewed by a Consultant Radiologist (blinded to cohort group) who determined percentage fibroid infarction in addition to uterine artery patency.

**Study Outcomes**

**Primary Outcome**

The primary clinical outcomes were percentage infarction of the dominant fibroid and all fibroid infarction rate. Infarction rate was classified into either complete infarction or incomplete infarction for both the dominant fibroid and for all fibroids, as determined by subjective assessment of a blinded consultant Radiologist.

**Secondary Outcome**

Uterine artery patency was the secondary outcome (also determined on the 3 month MRI by a Consultant Radiologist).

**Statistical Analysis**

Percentage fibroid infarct of the dominant fibroid (DF%) outcome was dichotomised two groups per embolic agent, 100% fibroid infarction and <100% fibroid infarction for purposes of the non-inferiority Chi square statistic which was used to assess for difference between the embolic groups. The same technique was used for the infarct percentage of all fibroids (AF%). The relative risk (RR) was calculated for presence of 100% fibroid infarct between cohorts. As mentioned in the sample size calculation, a difference of 33% (one third) was taken as the non-inferiority margin (RR >0.67 between the exposed group- Gelbead, and the ‘control’ groups- established embolic agents).

Analysis of Variance (ANOVA) statistical test was used to assess for underlying differences between the groups of patients in terms of age, initial uterine volume and initial dominant fibroid volume to assess for any potential confounding factors.

Analysis of variance (ANOVA) was used to assess for significant difference between uterine artery patency rates.

All Confidence Intervals reported are 95% confidence intervals, and a p value <0.05 was taken to represent a statistically significant result.

**Results**

Overall, 120 patients were included in this single centre study (n=20 per embolic agent). No significant difference was seen between baseline variables (table 1, figure 1a) across groups in terms of mean overall patient age (Embozenes 43.8, Beadblock 43.8, Gel-bead 44.6, Embosphere 46.2, Gelfoam 43.5, non-spherical PVA 47.1, p=0.39), mean initial uterine volume (Embozenes 547.8ml, Beadblock 687.1ml, Gel-bead 569.4ml, Embosphere 401.9ml, Gelfoam 539.5ml, non-spherical PVA 674.0ml, p=0.44), or mean initial dominant fibroid volume (Embozenes 249.2ml, Beadblock 355.0ml, Gel-bead 227.5ml, Embosphere 136.1ml, Gelfoam 174.4ml, non-spherical PVA 352.2ml, p=0.17).

 **Percentage Fibroid infarction**

Similar rates of percentage fibroid infarction were demonstrated between different embolic agents for both dominant fibroid infarction, (table 2, figure 2) (total (100%) infarction rates: Embozenes 17/20 (85.0%), Beadblock 15/20 (75.0%), Gel-bead 18/20 (90.0%), Embosphere 16/20 (80.0%), Gelfoam 17/20 (85.0%), non-spherical PVA 19/20 (95.0%) and all fibroid infarction (total (100%) infarction rates: Embozenes 14/20 (70.0%), Beadblock 13/20 (65.0%), Gel-bead 16/20 (80.0%), Embosphere 15/20 (75.0%), Gelfoam 14/20 (70.0%), non-spherical PVA 17/20 (85.0%).

When classified as a dichotomous outcome (100% or <100%), no significant difference was seen between the embolic groups in terms of dominant fibroid percentage infarction (Chi square test x2=3.92, p=0.56) or all fibroid infarction rate (x2 =2.83, p=0.73).

For complete Dominant Fibroid Infarction, non-inferiority (RR lower confidence interval >0.67) was demonstrated between Gel-bead and all other embolic agents (table 3, Embozenes RR 1.06, CI 0.84 - 1.34, Beadblock RR 1.20, CI 0.90- 1.61, Embosphere RR 1.13, CI 0.86- 1.45, Gelfoam RR 1.06, 0.84- 1.34, PVA RR 0.95, CI 0.79- 1.13, combined RR 1.07, RR 0.90- 1.27). Given a non-inferiority margin (d) of 0.67, p<0.05 for non-inferiority between Gel-bead and the other particles. This was also the case for Complete All Fibroid Infarction (Embozenes RR 1.14, CI 0.80- 1.64, Beadblock RR 1.23, CI 0.83- 1.82, Embosphere RR 1.07, CI 0.76- 1.49, Gelfoam RR 1.14, CI 0.80- 1.64, PVA RR 0.94, CI 0.71- 1.26, combined RR 1.09, RR 0.85- 1.41, d=0.67, p<0.05).

**Uterine Artery Patency Analysis of variance (ANOVA)**

In terms of uterine artery patency, Gel-bead was statistically different to Gelfoam, with a marginal mean difference of 55 % (82.5 vs. 27.5%, ANOVA *p*<0.001, after Bonferroni adjustment). No statistically significant difference was observed in terms of artery patency between Gel-bead and the other embolic agents (Embozenes 95.0%, Beadblock 92.5%, Embosphere 67.5%, PVA 82.5% uterine artery patency, ANOVA p=1.0 compared with Gel-bead after Bonferroni correction) as demonstrated by table 2 and figure 1d.

**Discussion**

Our previous case series of Gel-bead patients suggested this new, resorbable calibrated spherical agent had the potential to be a feasible option for patients undergoing fibroid embolization[(4)](https://paperpile.com/c/Yj4trw/p0Lp). However, our initial prospective study lacked a comparative analysis. This retrospective cohort study was planned as part of the initial study design to provide context to the Gel-bead patient cohort. Through this retrospective comparative analysis we have demonstrated that Gel-bead has similar outcomes in terms of fibroid infarct to other embolic agents (which is the best indicator of long term symptomatic outcome[(2,3)](https://paperpile.com/c/Yj4trw/ezMTy%2B4xLvZ), with evidence of non-inferiority of this calibrated, resorbable particle.

Whilst fibroid infarction rates in the Gelfoam slurry group are comparable with Gel-bead, the resorbable gelatin spheres demonstrated a statistically significantly greater potential to maintain MRI-determined uterine artery patency post-embolization. These differences may be due to a variable embolisation endpoint, with operators achieving more proximal stasis within the uterine artery with Gelfoam due to clumping of larger particles. No statistically significant difference was seen in uterine artery patency rates comparing Gel-bead against other ’permanent’ embolic agents.

A recent meta-analysis of comparative studies compared several frequently used embolics for UFE[(13)](https://paperpile.com/c/Yj4trw/wpiTH). Imaging outcomes in terms of complete dominant fibroid infarction were similar to our cohorts in this comparative study (studies included ranged from 33.3 to 92.3% total fibroid infarct). As infarct rates in our single centre study are similar to the meta-analysis, this suggests our results with Gel-bead are generalisable, with other operators likely to have similar outcomes. In terms of the secondary outcome of uterine artery patency, low rates of uterine artery patency post-embolization with gelatin slurry in this study is consistent with a recent randomised trial which found poor rates of uterine artery patency with Gelfoam[(10)](https://paperpile.com/c/Yj4trw/JsolM). Furthermore, studies examining uterine artery patency in permanent embolics [(10,14)](https://paperpile.com/c/Yj4trw/ViQkk%2BJsolM) also found a high rate of patency post-embolization (similar to our study). Therefore Gel-bead does not appear to hold a benefit over permanent agents with regards to uterine artery patency. A further important point to note is the lack of evidence regarding the significance of uterine artery patency. Although there are associations between occluded/ high resistance uterine arteries and fertility issues [(15,16)](https://paperpile.com/c/Yj4trw/a3Wsg%2BJxBEA), no studies specific to UFE, fertility and uterine artery patency have been performed to draw solid conclusions.

With regards to study limitations, this study only collected data on MRI-determined outcomes, and not clinical outcomes in terms of further surgery or symptom improvement through a validated questionnaire. The retrospective nature, the lack of randomisation and relatively small patient numbers are all features which further weaken the strength of the conclusions.

Gel-bead achieves an infarct rate comparable to other embolic agents and is therefore a good option for patients with symptomatic uterine fibroids.

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**Table and Figure Legends**

Table 1. Patient demographics per embolic cohort

Table 2. MRI outcomes post-embolization

Table 3. Relative risk of complete fibroid with Gel-bead compared against other embolic agents

Figure 1a. Patient age distribution per cohort, 1b. Initial dominant fibroid volume per cohort, 1c. Initial Uterine volume per cohort, 1d. MRI-determined uterine artery patency at 3 months per cohort

Figure 2a. Complete Dominant Fibroid Infarct rates per Embolic agent 2b. Complete All fibroid infarct rates per Embolic agent