

First Experience of Uterine Fibroid Embolization Using DC Bead® in Japan

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Abstract

Background: We performed uterine fibroid embolization (UFE) in four patients to assess the safety and efficacy of bland embolization using DC Bead®. They were the first patients in the world who underwent UFE procedure by using DC Bead®.

Methods: Four patients with uterine fibroids were enrolled and super selective embolization with DC Bead® was performed in a Japanese clinical trial. Efficacy, success rate of embolization in the target vessel (embolic performance) and operability were evaluated. To evaluate the safety, adverse events and device deficiency occurring within 30 days after the embolization were collected.

Results: Patient's age range was 34 to 48 years old. Uterine fibroid size range was 40 to 108 mm (maximum length of diameter). Multiple tumors were found in all cases. DC Bead® size range was 100-300 µm to 500-700 µm.

In the evaluation of embolic performance, three cases were completely embolized (100% disappearance of target vessel and staining on DSA) and one case was highly embolized (80% or more disappearance of target vessel, stained on DSA). In the evaluation of operability, all cases were evaluated as very easy to use. At 3, 6, 12 months after embolization, shrinkage in all uterine fibroids could be seen. The largest reduction rate was 59% in size (the mean was 43%).

Post embolization syndrome was observed in all patients. However, the degree of these was mild or moderate (grade 1 or 2 of CTCAE version 4.0). There was no serious adverse event.

Conclusions: Uterine fibroid embolization using DC Bead® was safely and successfully performed. DC Bead® will be a useful embolic material for uterine fibroid embolization.

Keywords: Uterine; Fibroid; Embolization; DC bead; Microsphere

Introduction

Uterine fibroid is a benign tumor found approximately in one out of five women between the ages of 30's and 40's. Although uterine fibroids may not be fatal or life-threatening, it can cause heavy bleeding and cramps during the menstruation, severely affecting a women's quality of life. While hysterectomy is the most common treatment approach for uterine fibroids, other options such as medication, hormone therapy, or uterine artery embolization (UAE) can be considered for patients who refuse to undergo or are not amenable to the surgical procedure.

Since UAE was introduced by Ravina et al. in 1995 [1], it has been a common procedure indicated for patients with uterine fibroids in the US and other countries. UAE is also proven to be effective to reduce massive bleeding during a delivery. In Japan, UAE using gelatin sponge particles or acrylic polymer microspheres impregnated with porcine gelatin is performed in some medical institutions [2].

DC Bead® (Biocompatibles UK Ltd, a BTG International group company), produced from polyvinyl alcohol (PVA) macromere, is widely used for transcatheter arterial chemoembolization in patients with hepatocellular carcinoma. In Japan, DC Bead® is indicated for the treatment of hepatocellular carcinoma and we aim to extend this indication to include hypervascular tumor. We performed uterine fibroid embolization (UFE) in four patients to assess the safety and efficacy of bland embolization using DC Bead®.

Material and Methods

Between May 2013 and September 2013, four patients with uterine fibroids were enrolled and super selective embolization with DC Bead® was performed in a Japanese clinical study.

Screening assessments were performed by the investigator on those who gave a written informed consent for this study. Japanese subjects with uterine fibroid in which arterial embolization is indicated, who meet all of the inclusion criteria and none of the exclusion criteria were eligible for this study. Main Inclusion Criteria:

- Patients have a uterine fibroid that are not amenable to resection or refuse to undergo resection.
- At low risk of embolic material entering the systemic circulation and the size of arteries supplying the lesion is appropriate for the microsphere embolization confirmed by CT imaging.
- Are given full explanation of safety, expected efficacy and involved risks with DC Bead® and UAE Embolization procedure Prior to the procedure, condition of target vessel was evaluated by angiography and CT. Optimal volume and size (100 to 300 µm, 300 to 500 µm, 500 to 700 µm) of microsphere that best matches the pathology (i.e., vascular target, vessel size) were carefully selected. A delivery catheter that matches the particle size was introduced into the target vessels, and DC Bead® adequately mixed in contrast medium

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Received September 25, 2015; **Accepted** September 27, 2015; **Published** October 05, 2015

Citation: Yodono H, Saito Y, Maeda S (2015) First Experience of Uterine Fibroid Embolization Using DC Bead® in Japan. J Women's Health Care 4: 278. doi:10.4172/2167-0420.1000278

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was slowly injected. The injection was stopped when vascular stasis in the target vessel was confirmed after careful evaluation of the treatment site.

Efficacy

Success rate of embolization in the target vessel (embolic performance) and operability were evaluated. Embolic performance was assessed with digital subtraction angiography (DSA) by a third party (DSA Imaging Evaluation Committee). Embolic performance and operability were each graded in 4 degrees as shown below.

Operability and usability were evaluated by the investigator on the basis of the sense of resistance when DC Bead was injected, and how smoothly the microspheres could pass through the catheter. The evaluation criteria are:

- Very easy to use
- Easy to use
- Difficult to use

- Very difficult to use

Treatment progress evaluated by magnetic resonance imaging (MRI) was surveyed at 3, 6, and 12 months after arterial embolization therapy (Table 1).

Safety

All adverse events (symptoms, laboratory evaluation of hematology, blood chemistry, coagulation, and urine tests; body weight, vital signs and 12-lead ECGs) were collected within 30 days after arterial embolization. Condition of tumor, survival, etc. was surveyed at 3 months after the embolization (Table 2).

Results

Patient demographics are shown in Table 3.

Age range was 34 to 48 years old, uterine fibroid size range was 40 to 108 mm (maximum length of diameter). Multiple tumors were found in all cases. DC Bead® size range used in the UFE procedure was 100-300 µm to 500-700 µm.

Completely embolized	100% disappearance of target vessel and staining on DSA after embolization
Highly embolized	80% or more disappearance of target vessel, staining on DSA after embolization
Moderately embolized	50% or more to below 80% disappearance of target vessel and staining on DSA after embolization
Relatively embolized	Less than 50% disappearance of target vessel and staining on DSA after embolization

Table 1: Criteria for Embolic performance.

Patient No.	Size range of DC Bead® (µm)	Embolic performance	Operability	Adverse events	Reduction ratio (%)		
					After 3M	After 6M	After 12M
01	100-300 300-500 500-700	Completely embolized	Very easy to use	Yes	28	30	29
02	100-300 300-500	Completely embolized	Very easy to use	Yes	40	50	89
03	100-300 300-500 500-700	Completely embolized	Very easy to use	Yes	59	62	ND*
04	100-300 300-500 500-700	Completely embolized	Very easy to use	Yes	45	60	72

*ND: Not determined.

Table 2: Efficacy and Safety.

Patient No.	Age	Maximum length of Fibroid diameter	complication	shunt
01	40	108 mm	Iron deficiency anemia	none
02	34	40 mm	Bronchitic asthma Allergy coryza	none
03	48	72 mm	Iron deficiency anemia Hay fever	none
04	41	69 mm	Iron deficiency anemia	none

Table 3: Patients demographics.

Patient No.	Adverse events
01	Post embolization syndrome (1)* ,Pelvic pain(2), Decreased appetite(2), Somnolence(1), Dizziness(1)
02	Post embolization syndrome(1) , Pelvic pain(2), Decreased appetite(2), Nausea, Vomiting(1), Constipation, Ovarian haemorrhage(1), Lymphocyte count decreased (2)
03	Post embolization syndrome(1) , Pelvic pain(2), Decreased appetite(2), Nausea(2), Vomiting(2), Dizziness(1), Lymphocyte count decreased(2), Hypocalcaemia(2), Aspartate aminotransferase increased(2), Alanine aminotransferase increased(2)
04	Post embolization syndrome(1) , Pelvic pain(2), Decreased appetite(2), Nausea(1), Vomiting(1), Uterine hemorrhage (2), Lymphocyte count decreased(2), Alanine aminotransferase increased(2)

*Grade of CTCAE version 4.0.

Table 4: Adverse events.

In the evaluation of embolic performance of target vessels by the Imaging Evaluation Committee, three cases were judged to be completely embolized (100% disappearance of target vessel and staining on DSA), one case was judged to be highly embolized. In the evaluation of operability of embolization, all cases were judged to be very easy to use. No device deficiency had occurred in four patients. Although post embolization syndrome was observed in all patients, they were all mild or moderate cases (grade 1 or 2 of CTCAE version 4.0). A list of AEs is shown in Table 4. There was no occurrence of serious adverse event. Events except a part of pelvic pain had disappeared within 30 days after embolization. The pelvic pain that did not disappear had recovered within 30 days after embolization (Figures 1 and 2).

At three months after embolization using DC Bead, 92% of the fibroid was necrotized. At six months after embolization, the size of the fibroid decreased by almost 30% as evaluated by 3D-MRI (Figures 3-5).

At three months after embolization using DC Bead, 100% of the fibroid was necrotized. At six months after embolization, the size of the

fibroid decreased almost by 62% as evaluated by 3D-MRI (Figure 6).

Limitation

Because of small number of patients, we did not analyze the confounding factor in this study.

Furthermore, the small sample size led to limitations on performing multivariate regression analyses to detect the confounding factor.

Discussion

Embolic materials commonly used in Japan have been causing occasional aggregation or blockage of a catheter during an embolization procedure. In order to completely embolize the target vessels without clogging the catheter, the device has to be smoothly delivered through the catheter while surely remaining at the target site without migrating to non-target vessels.

DC Bead®, widely used in the treatment of hyper vascular tumors in US, Europe and Japan, is a high-performing embolic material

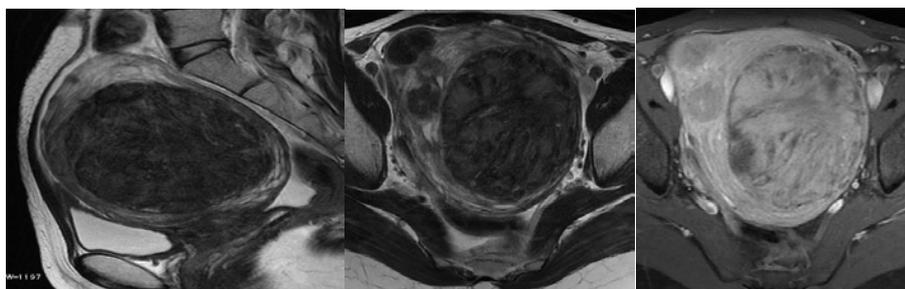


Figure 1: MRI of Case 1 before UFE. CASE 1: 40-year-old woman had the 108 mm size uterine fibroid.

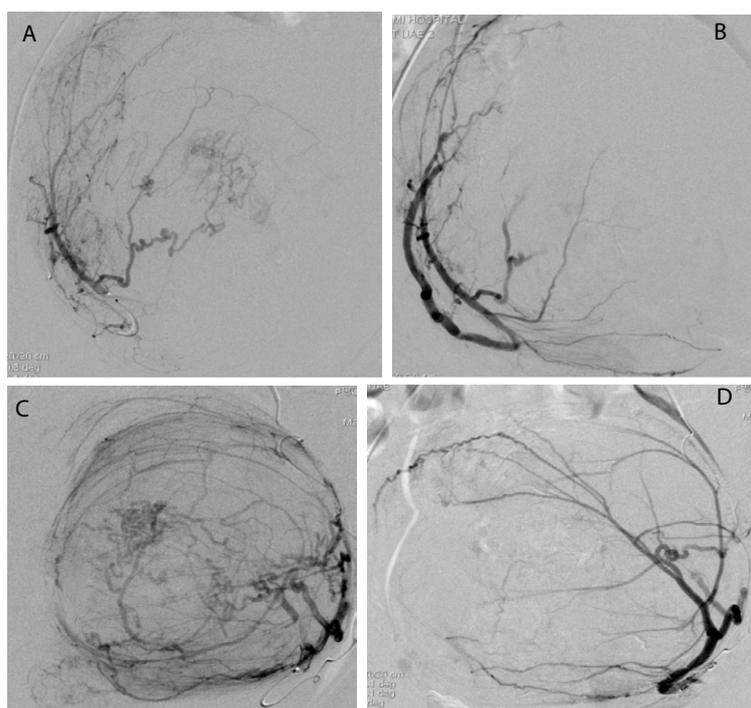


Figure 2: DSA of Case 1. (a) Pre-embolization right uterine artery (UA), (b) Post right UA, (c) Pre left UA, (d) Post left UA.

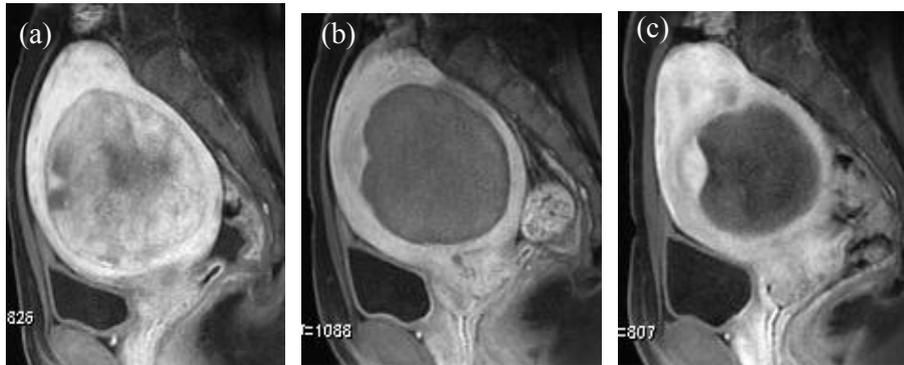


Figure 3: MRI of case 1 before and after UFE. (a) pre-operation, (b) 3 M after embolization, (c) 6 M after embolization.

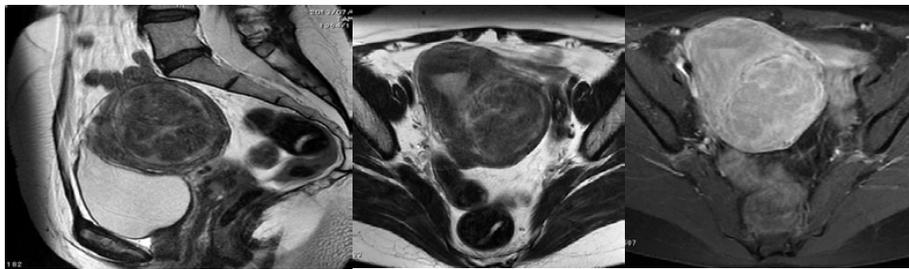


Figure 4: MRI of Case 3 before UFE. Case 3: 48-year-old woman had the 72 mm size uterine fibroid.

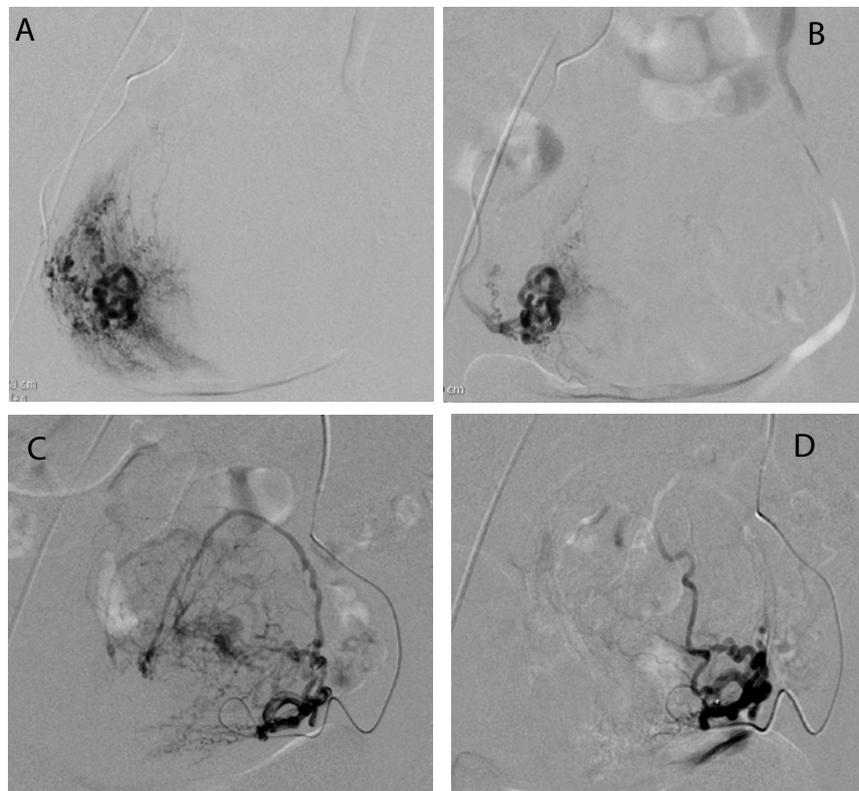


Figure 5: DSA Case 3: (a) Pre-emboliz right uterine artery (UA), (b) Post right UA, (c) Pre left UA, (d) Post left UA

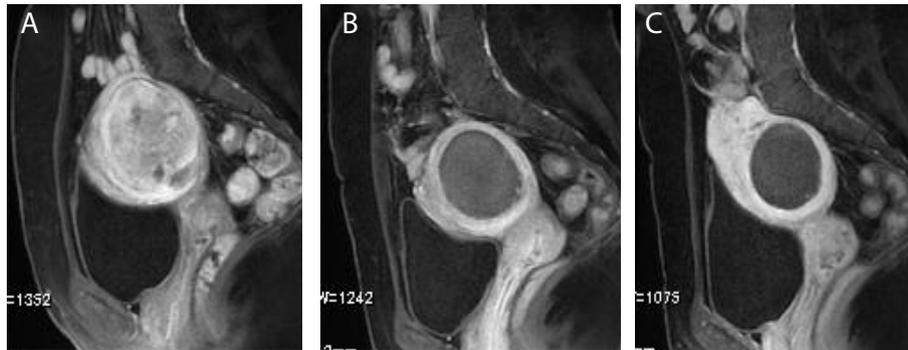


Figure 6: MRI before and after UFE. Case 3: (a) pre-operation, (b) 3 M after embolization, (c) 6 M after embolization.

characterized by its ability to elute some anticancer drugs by an irreversible ionic bond [3]. In addition, DC Bead® is more rigid and less deformable compared to other PVA embolic materials, thus making it less likely to migrate into the peripheries and easier to predict the embolization effect.

These properties and characteristics of DC Bead® can be safely and effectively adopted for UFE procedures, to embolize uterine arteries without device migration to non-target vessels such as the ovarian arteries. UFE, similar to other artery embolization procedures, blocks the blood supply into the tumors thus causing them to necrotize, resulting in tumor size reduction and relief of associated symptoms.

While hysterectomy or myomectomy is the first-line treatment choice for treating uterine fibroids, UFE may be indicated for patients who do not desire surgery or may be poor surgical candidates; e.g. risk of developing complications.

According to the previously conducted study in 135 patients with uterine fibroids, Suzuki reported that there was no significant difference in effectiveness and occurrence of adverse events between procedures using gelatin sponge particles and polyvinyl alcohol microspheres, considering them as equally useful as surgical procedures [4]. UFE is also recommended by ACOG (The American College of Obstetricians and Gynecologists) as a safe and effective option for appropriately selected women who wish to retain their uteri [5].

Furthermore, a meta-analysis performed by Sandeep et al. on 8159 patients with uterine fibroids reported that serious complications occurred in 2.9%, which was similar to the results of patients who underwent surgical procedures [6]. Of those, only 0.7% required medical interventions such as total hysterectomy. When compared with other polyvinyl alcoholic embolization materials, occurrence of severe complications were 2.8%, with similar results as gelatin sponge particles (3.6%) and Embosphere® Microspheres (2.3%).

For the patients who underwent UFE procedure with DC Bead®, three sphere sizes ranging from 100 to 700 µm were selected to effectively treat various conditions: multiple tumors with separate blood supplying vessels and various vessel sizes. As a result, there were no serious issues including device migration to ovarian arteries or other notable complications. Extent of embolization was relatively small and post-embolization syndrome was only at mild degree with minimal discomfort and pain experienced by patients.

In all patients, associated conditions such as heavy menstrual bleeding, dizziness and pelvic pain were relived and their QOL has

significantly improved. The tumor size assessed by 3-D image tumor volume calculation showed reduction in all patients (by 30%, 50%, 59% and 32%) at six months post-embolization.

Although the population size for this evaluation was small (four), the safety and effectiveness of procedure using DC Bead® for treatment of uterine fibroids was well demonstrated.

Acknowledgments

This research was sponsored by Eisai Co. Ltd.

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