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Original Article

Tri-acryl gelatin microsphere is better than polyvinyl alcohol in the treatment of uterine myomas with uterine artery embolization

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Abstract: This study is to compare the outcomes of tri-acryl gelatin microspheres (TAGM) and polyvinyl alcohol (PVA) in the treatment of uterine myomas with uterine artery embolization (UAE). Meta-analysis was performed by electronic literature searches from databases including Cochrane Central Register of Controlled Trials, PubMed, EMBASE and meta Register of Controlled Trials for studies published prior to December 2014. Randomized controlled trials comparing TAGM and PVA treating uterine myomas were included in the analysis. Information retrieved from each study included study design, number of participants, study settings, patient characteristics, sample size, follow-up duration and outcomes. Imaging outcomes and clinical outcomes were the main criteria for the evaluation of the included studies. Twenty-eight articles published from 1966 to December 2014 were retrieved through database searching and other sources. After initial screening and assessment, five randomized controlled trials, including 309 women with uterine myomas, met the inclusion criteria. In both imaging and clinical outcomes, TAGM group showed superior or similar effects than PVA group. The results showed more number of patients with significant tumor enhancement, greater mean change in tumor volume, greater mean changes in symptom score and QOL score in TAGM group compared with PVA group, with significant differences. TAGM and PVA groups had similar uterine volume, mean changes in bleeding score and pain score. TAGM is better than PVA as an embolic agent in the treatment of uterine myomas with UAE.

Keywords: Tri-acryl gelatin microsphere, polyvinyl alcohol, uterine myomas, uterine artery embolization, meta-analysis

Introduction

Uterine myomas, which are the most common gynecological benign tumors, can cause pain, bleeding symptoms such as menorrhagia and metrorrhagia, pressure symptoms and subfertility. They are typically discovered in the late reproduction period and are present in up to 40% of women after the age of forty [1]. Surgical therapies for uterine myomas are associated with long-term problems such as fibroid recurrence, adhesion formation and increased possibility of uterine rupture during pregnancy and vaginal delivery [2]. There is a strong need for effective non-surgical therapies for uterine myomas.

Since uterine artery embolization (UAE) became a potential treatment for menorrhagia in 1995 [3, 4], increasing numbers of literatures supported UAE as a treatment for uterine myomas [5-8]. UAE, as a safe and minimally invasive alternative to surgery, is a newer treatment option that blocks blood supply to the uterus and shrinks uterine myomas. Spies J [9] speculated that aspects of recovery (particularly pain) might be associated with the physical characteristics of different embolic materials. The choice of embolic agents during UAE is controversial. Meanwhile, it is important to understand the effectiveness and relative advantages of different embolic agents [10-12]. Tris-acryl gelatin microspheres (TAGM) and polyvinyl alco-

Table 1. Search results

Search string*	Embase	PubMed	Meta register of controlled trials	Cochrane central register of controlled trials	
Number of results	13	9	1	Cochrane reviews	0
				Clinical trials	5
				Technology assessments	0
Total			28		

Note: *, Polyvinyl alcohol AND tris acryl AND (fibromyoma OR leiomyomata OR myoma OR leiomyoma OR uterine fibroid) AND (Uterine artery occlusion OR Uterine artery embolisation OR uterine artery embolization OR UAE) AND (randomised OR randomized).

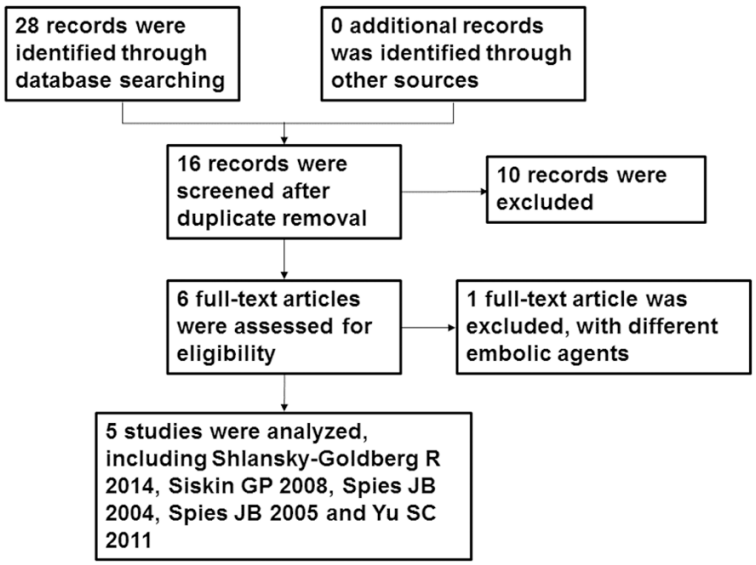

Figure 1. Flow chart of meta-analysis.

hol (PVA) are two commonly used embolic agents in UAE for the treatment of leiomyomas [13]. Trials comparing the two embolic agents have been inconclusive in terms of clinical benefits. The most commonly used agent is polyvinyl alcohol (PVA), a non-biodegradable agent. Some animal studies [14, 15] confirmed the efficacy of PVA as an embolic agent before its general release. In addition, a multicenter clinical trial [16] demonstrated that PVA used for UAE in the treatment of patients with symptomatic uterine myomas significantly alleviated tumor-related symptoms and improved health-related quality of life in addition to significant reductions in uterine and tumor volumes. However, nonspherical PVA, which is initially used for UAE, showed many shortcomings, including inherent size variability in particle preparations, difficulty of injecting particulate PVA through a microcatheter, and clumping of particles that makes the effective size of PVA larger than the actual size, leading to embolic occlusion that is more proximal than intended [10, 17-19]. Therefore, spherical PVA was developed against the tendency to clump and obstruct microcatheters. TAGM are solid microspheres of acrylic copolymer that is cross-linked to gelatin [13]. As a spherical embolic agent, TAGM was introduced and almost immediately used as an embolic agent of UAE for the treatment of uterine myomas. Single-center retrospective studies and multicenter clinical trials [11, 20-23] have confirmed the success of TAGM. In this study, we carried out meta-analysis of available evidences to compare TAGM and PVA microspheres in uterine artery embolization for the treatment of uterine myomas.

Materials and methods

Search strategy

Using the search strategy outlined by the Cochrane Collaboration [24, 25], we searched for relevant studies in databases including Cochrane Central Register of Controlled Trials (The Cochrane Library; Wiley InterScience), PubMed, EMBASE and meta Register of Controlled Trials, from the earliest records up to December 2014. The following search string was used: polyvinyl alcohol AND tris acryl AND (fibromyoma OR leiomyomata OR myoma OR leiomyoma OR uterine fibroid) AND (Uterine artery occlusion OR Uterine artery embolization OR uterine artery embolization OR UAE) AND (randomized OR randomized). There was no language restriction.

Selection criteria

The inclusion and exclusion criteria used in selecting the procedures were: i) target population: premenopausal adult patients with symp-

Table 2. Demographic information

Studies	Origin of target population	No. of patients (TAGM/PVA)	Duration of follow-up	Age (years) (TAGM/PVA)	Funds
Shlansky-Goldberg R 2014 [31]	USA	30/30	3 and 12 months*	41.7 ± 5.4/43.9 ± 5.0	Funded by Boston Scientific (Natick, Massa-chusetts)
Siskin GP 2008 [26]	USA	27/26	6 months	44.9/45.0	Not described
Spies JB 2004 [32]	USA	54/46	3 months	43.4 ± 5.4/42.5 ± 5.0	No
Spies JB 2005 [33]	USA	19/17	3 months	45.9 ± 4.4/44.9 ± 6.2	No
Yu SC 2011 [13]	Hong Kong	30/30	3 and 9 months*	40.3 ± 5.1/42.7 ± 5.15	Not described

Note: *, Shlansky-Glodberg et al. presented 3- and 12-month outcomes after treatment [14], and Yu et al. presented 3- and 9-month outcomes [9]. To reduce bias by relatively consistent follow-up, 3-month outcomes were included in the meta-analysis.

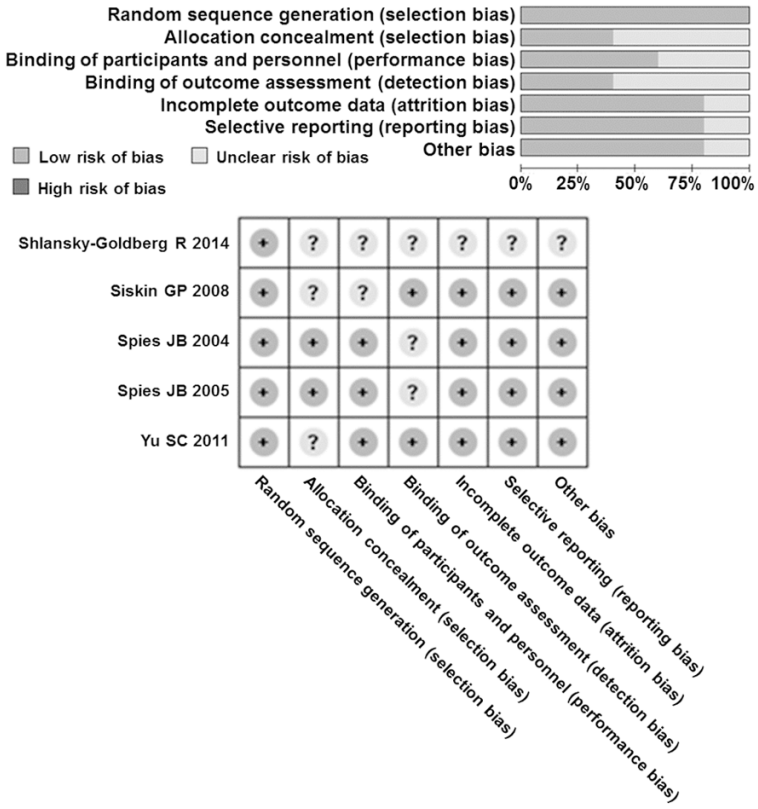

Figure 2. Risk of bias in included studies. Statistical software Review Manager 5.0 (Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark) was used for the analysis.

tomatic leiomyomas; ii) intervention: trials comparing TAGM and PVA were included; iii) methodological criteria: randomized controlled trials that compared TAGM and PVA. If the same study (conducted at the same institution and/or by the same authors) was reported twice in different journals, the paper published in the journal with the highest impact factor or the most recent publication was included in the analysis.

Two reviewers independently performed initial screening, extraction, and assessment of all studies based on eligibility of inclusion. Controversies were discussed by another reviewer. Information retrieved from each study included study design, number of participants, study settings, patient characteristics, sample size, follow-up duration and outcomes. Imaging outcomes (the number of patients with significant tumor enhancement, mean change in uterine volume, and mean change in tumor volume) and clinical outcomes (mean changes in symptom score, quality of life (QOL) score, bleeding score, and pain score) were the main criteria used by meta-analysis to evaluate the included studies. Significant tumor enhancement was defined as >10% of the overall burden [26].

Statistical analysis

Meta-analysis was performed according to recommendations from QUORUM [27], MOOSE [28], and Cochrane Collaboration [29]. Using the statistical software Review Manager 5.0 (Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark), relative risk (RR) in each study was calculated for dichotomous outcomes, while weighted mean difference (WMD) was calculated for continuous outcomes, both adopting a 95% confidence interval (CI).

Heterogeneity among studies was tested using Chi-square test and I-square test [30]. A significant level less than 0.10 for Chi-square test

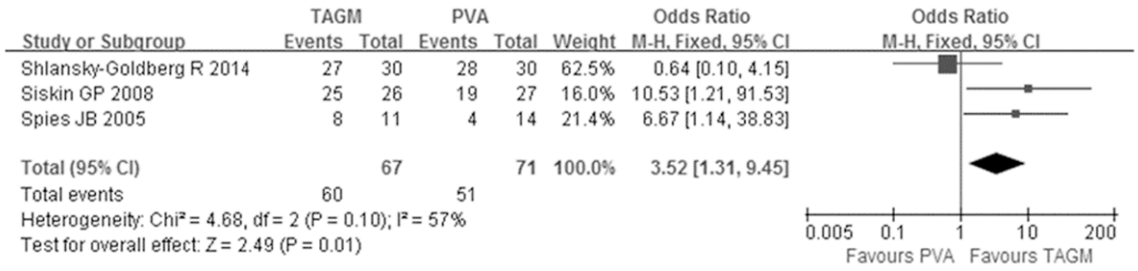

Figure 3. Forest plot of studies and comparison of number of patients with significant tumor enhancement between TAGM and PVA. Statistical software Review Manager 5.0 (Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark) was used for the analysis.

was interpreted as evidence of heterogeneity and I-square was used to estimate total variation across studies. Where there was no statistical evidence of heterogeneity, a fixed effect model was adopted. Where there was statistical evidence of heterogeneity, a random effect model was used. The possibility of publishing bias was not included due to the small number of studies included.

Results

Demographic data

In order to perform meta-analysis to compare TAGM and PVA microspheres in uterine artery embolization for the treatment of uterine myomas, 28 articles published from 1966 to December 2014 were retrieved (**Table 1**). After abstract screening and full-text screening, 5 studies were included in this study (**Figure 1**). Demographic information showed that four trials were in America and one trial was in Hong Kong. All five trials had small-sized population. The durations of follow-up of five trials showed differences. To reduce bias by relatively consistent follow-up, 3-month outcomes by Shlansy-Goldberg et al. in 2014 and Yu et al. in 2011 were included in the meta-analysis. Ages were comparable and no explicit funds were provided for all five trials (**Table 2**). The results suggest that demographic data at baseline are similar.

Risk of bias in included studies

To assess the quality of the five eligible randomized controlled trials, component approach was used to check the methodological aspects of each trial with the criterion recommended by Cochrane. Inevitably, some risk of bias was likely due to difficulties in allocation concealment and blinding in these studies. Requests to the trial investigators of all five trials for clarification of study methods were unsuccessful (**Figure 2**). All five trials were randomized into two groups with explicit randomization methods. Allocation concealment was not descried in three trials [13, 26, 31]. Blinding of participants and personnel was not described in two trials [26, 31]. Otherwise, blinding of outcome assessment was not described in three trials [31-33]. In addition, incomplete outcome, selective reporting and other bias were not described by Shlansky-Goldberg et al. [31]. Although these trials appeared to be at low risk of selection, attrition and reporting bias, they were judged at medium risk of selection, performance and detection bias. Therefore, all five studies were at some risk of various biases and the quality of the evidence was at “medium”.

Imaging outcomes

To compare the imaging outcomes between TAGM and PVA microspheres in uterine artery embolization for the treatment of uterine myomas, the number of patients with significant tumor enhancement, mean change in uterine volume, and mean change in tumor volume were investigated. The number of patients with significant tumor enhancement was provided in two studies. Three studies showed a total of 138 patients, including 67 patients in TAGM group and 71 in PVA group [26, 31, 33]. Meta-analysis showed that there was significant difference in the number of significant tumor enhancement between TAGM and PVA (RR: 3.52, 95% CI: 1.31-9.45, P=0.01) (**Figure 3**). In addition, mean change in uterine volumes was studied in two studies [32, 33] and mean

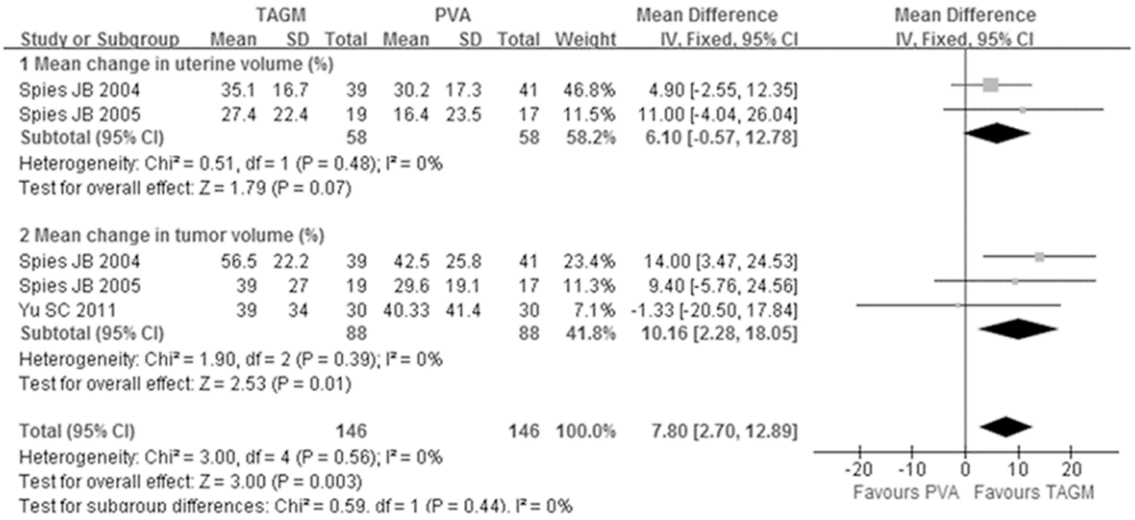

Figure 4. Forest plot of studies and comparison of mean change in uterine and tumor volumes between TAGM and PVA. Statistical software Review Manager 5.0 (Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark) was used for the analysis.

change in tumor volumes was reported in three studies [13, 32, 33] (**Figure 4**). Meta-analysis demonstrated that there was no significant difference in mean change in uterine volume between TAGM and PVA (WMD: 6.10, 95% CI: -0.57-12.78, P=0.07). However, there was significant difference in mean change in tumor volume between TAGM and PVA (WMD: 10.16, 95% CI: 2.28-18.05, P=0.01). These data suggest that TAGM group shows superior effects than PVA group in imaging outcomes.

Clinical outcomes

To compare the imaging outcomes between TAGM and PVA microspheres in uterine artery embolization for the treatment of uterine myomas, mean changes in symptom score, QOL score, bleeding score, and pain score were studied. Mean changes in symptom, QOL, bleeding and pain scores were provided in two studies (Spies JB 2004 [32] and Spies JB 2005 [33]), which showed a total of 136 patients, including 73 patients in TAGM group and 63 in PVA group. Meta-analysis showed significant differences in mean changes in symptom and QOL scores between TAGM and PVA (WMD: 12.37, 95% CI: 4.10-20.65, P=0.003; WMD: 15.19, 95% CI: 7.04-23.33, P=0.0003), while similar mean changes were observed in bleeding and pain scores between the two (WMD: 0.19, 95% CI: -0.37-0.75, P=0.50; WMD: 0.08, 95% CI: -0.50-0.67, P=0.78) (**Figure 5**). These data suggest that TAGM group shows superior effects than PVA group in clinical outcomes.

Discussion

Meta-analysis was designed to investigate which embolic agent, TAGM or PVA, was the better choice for UAE for the treatment of uterine myoma. In this study, TAGM group had better number of patients with significant tumor enhancement and greater mean change in tumor volume than PVA group. Furthermore, TAGM group had greater mean change in symptom score and QOL score than PVA group did.

Based on previous imaging literatures [34-36], investigators categorized patients with peripheral rim enhancement as having 100% infarction after embolization. Siskin GP [26] and Spies JB [33] showed more significant tumor enhancement (defined as the degree of infarction >90% of the overall burden) when using TAGM. The rate of significant tumor enhancement in the TAGM group was 96.2% in Siskin GP [26] and 72.7% in Spies JB [33], with the rate of significant tumor enhancement in the PVA group being 70.4% in Siskin GP [26] and 28.6% in Spies JB [33]. Although Shlansky-Goldberg et al. showed more significant tumor enhancement when using PVA (89.3% in TAGM group and 92.8% in PVA group) [31], more patients with 100% infarction were in TAGM

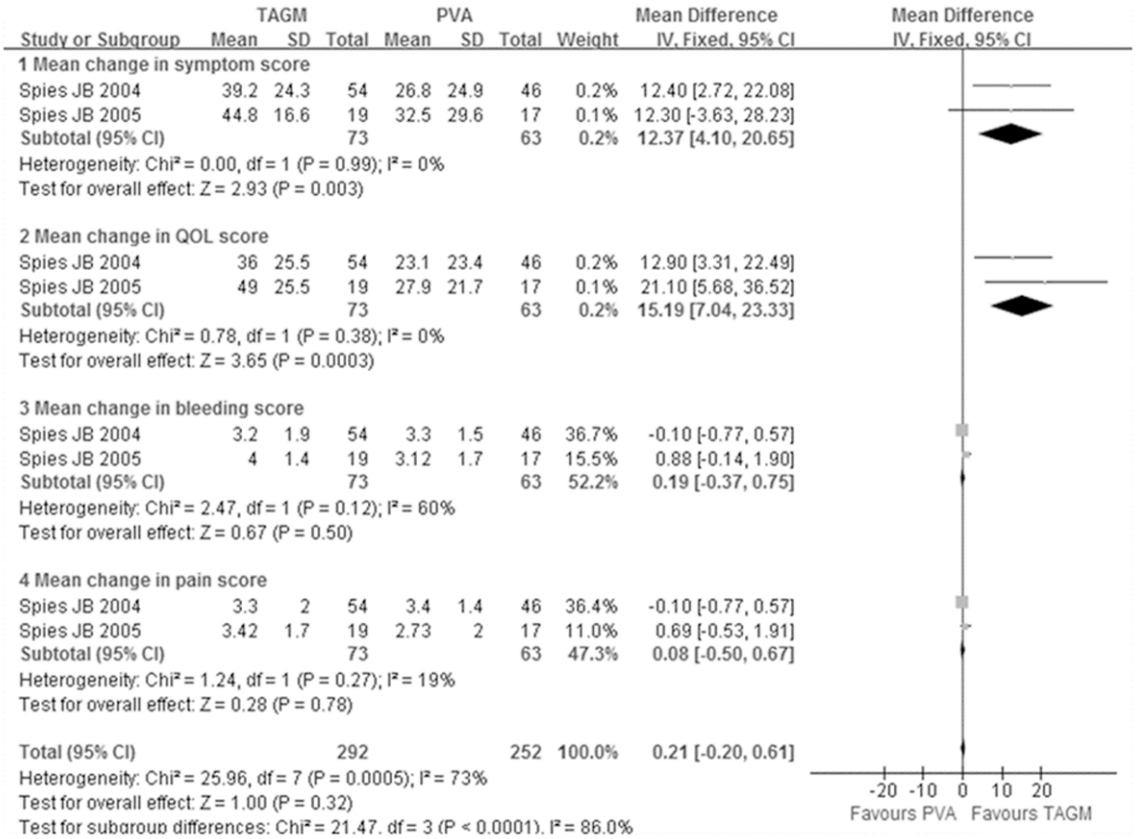

Figure 5. Forest plot of studies and comparison of mean change in symptom, QOL, bleeding and pain scores between TAGM and PVA. Statistical software Review Manager 5.0 (Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark) was used for the analysis.

group (85.7% in TAGM group and 82.1% in PVA group). Imaging failures led to premature termination of the trial according to Spies and his colleagues [33]. Compared with UAE with PVA microspheres, UAE with TAGM was more likely to cause at least 90% tumor infarction, and was associated with a lower mean percentage of residual perfusion of tumor tissue. Incompletely infarcted fibroids were related with limited relief of symptoms, which was in accordance with the clinical outcomes. A recent study by Pelage and colleagues [37] showed that incompletely infarcted fibroids were associated with regrowth and recurrent symptoms. Using meta-analysis, lower rate of regrowth and recurrent symptoms was observed when using TAGM.

Based on these surprising outcomes, studies were designed to explain why PVA was related to unsatisfactory clinical and imaging outcomes. Initial nonspherical PVA particles do not completely block the lumen of the occluded arteries due to their irregular shapes and heterogeneous calibration [38]. The occlusion of artery is caused by thrombus formation and leads to unpredictable embolization and variable levels of arterial occlusion [39]. Based on these, spherical PVA particles were developed. Siskin et al. [15] found that spherical PVA particles penetrated more distally during experimental embolization compared with other embolic agents with similar size. The reason may be that spherical PVA deforms, flattens, or otherwise assumes a smaller profile after embolization, resulting in shifting of the material more distally in the vessels. As a result of this finding, Pelage [40] reported desired outcomes that complete tumor infarction occurred in 83% patients when using larger PVA microspheres with UAE. The key points were larger PVA microspheres (700-900 μm), a more aggressive angiographic endpoint approaching stasis, and a 5-minute waiting period after embolization of each uterine artery to confirm

that the vessel remained embolized before the catheter was removed from the vessel. This became known as the refined protocol by the manufacturer of these microspheres and was incorporated into the instructions for use of the products [26].

PVA are more compressible than TAGM. This might be why TAGM showed better imaging outcomes. An *in vitro* study [41] showed that forces required to compress tris-acryl microspheres were in the range of 21-27.5 kPa, whereas PVA microspheres were significantly more compressible (about 5 kPa). Similar results were observed in an animal study [15]. Relatively greater compressibility of PVA could result in more distal redistribution of embolic agent into the tumor or uterine branches. Finally, PVA allowed partial revascularization of portions of the fibroid tumor tissue and increased the rate of regrowth and recurrence of uterine myomas.

Meanwhile, Yu et al. [13] compared TAGM and PVA in terms of inflammatory and stress responses as well as clinical manifestations, but found no significant difference. In addition, TAGM showed advantages in clinical outcomes. In meta-analysis, changes in symptoms and QOL scores in TAGM group were greater than those in PVA group.

To summarize, only five studies were included in the meta-analysis according to strict methodological criteria. Meta-analysis showed that the outcomes of TAGM were superior (better number of significant tumor enhancement, greater mean change in tumor volume, greater mean changes in symptom and QOL scores) or equivalent (similar uterine volume and mean changes in bleeding and pain scores) to those of PVA.

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Disclosure of conflict of interest

None.

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