

The EMMY Trial of Uterine Artery Embolization for the Treatment of Symptomatic Uterine Fibroid Tumors: Randomized, Yes, but a Flawed Trial Nonetheless

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Abbreviations: EMMY = Embolization versus hysterectoMY (Trial), PVA = polyvinyl alcohol

IN this issue of *JVIR*, an analysis of the short-term results of the EMMY Trial (Embolization versus hysterectoMY) is published, focusing on the technical outcome of the procedure (1). This article is one of an anticipated series of reports of a randomized trial from The Netherlands comparing the outcomes from uterine artery embolization (UAE) versus those of hysterectomy. The first of the publications from this trial appeared in November 2005 in the *American Journal of Obstetrics and Gynecology* and focused on the recovery and short-term outcome from the procedure (2). As certain aspects of the study design are described better in the earlier publication, this commentary will review the results from both these publications.

The study is a randomized trial to compare outcomes from the two procedures, with 177 patients enrolled (88 treated with UAE and 89 treated with hysterectomy). The primary endpoint of the study was the elimination of menorrhagia after a follow-up period

of 2 years, with UAE considered equivalent to hysterectomy if menorrhagia resolved in at least 75% of patients with no significant differences in major complications between the two procedures. A power analysis yielded a requirement of 120 total patients to be included. Although that calculation was based on the 2-year outcome, the two initial reports focus on a number of short-term measures for which no separate power analysis was completed.

The report in the *American Journal of Obstetrics and Gynecology* reported the following key findings (2): The technical failure rate for the procedure was significantly higher with UAE, bilateral UAE failed in 4.9% of patients, and an additional 6.2% patients had a unilateral technical failure. Major complications occurred in 4.9% of patients in the UAE group and 2.7% in the hysterectomy group, incidences that were not significantly different ($P = .68$). They did find that UAE was significantly more likely to result in minor complications (58% vs 40%; relative risk, 1.45; $P = .024$). The difference in minor complications occurred in the follow-up phase of the study during the first 6 weeks after discharge, with adverse events much more likely in the UAE group. Although the total length of stay was shorter for patients who were treated with UAE (mean,

2.5 days vs 5.1 days; $P < .001$), patients in the UAE group were readmitted more often (11.1% vs 0; $P = .003$), with most readmissions within the first several days after discharge.

Additional analysis is provided in the publication in this issue of *JVIR* (1). In this article, the authors report a technical failure rate of 5.3% and a procedural failure rate of 17.3%. In this set of definitions, a technical failure is one in which bilateral uterine tumor arterial supply is not occluded. A procedural failure is a procedure in which bilateral embolization was not completed for any reason and includes those with an absent uterine artery (with ovarian artery replacement not treated), those with no uterine artery flow after catheterization, and those with extensive collateral vessels to the vagina or cervix, in addition to the technical failures. The frequency of incomplete embolization in this group of patients raises concerns about the clinical outcomes that will be noted 2 years after therapy when the trial is concluded.

Based on these two articles, authors have reached the following initial conclusions: there is a higher than previously reported technical failure rate for UAE, postdischarge complications are more likely for patients treated with UAE, and there is a higher readmission rate among patients treated with UAE. In the article in this journal

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(1), the authors further conclude that the use of a larger amount of embolization material is associated with increased risk of postintervention fever, major complications, and severe pain. These results are the opposite of those found in a previously published multicenter nonrandomized comparison of UAE versus hysterectomy (3), which found that complications were more likely after hysterectomy.

The authors explain the differences in their key findings compared with those of other published studies by first suggesting that most earlier series have been from specialized centers, with results not likely achievable in broader practice. They believe that their results reflect a more realistic view of outcome in general practice. Second, the authors suggest that, because their results are from a randomized study, they are more valid than those from trials with nonrandomized designs, and they note that case series are more prone to "publication bias and patient selection criteria" in these interventions (2). The implication is that the poorer results they found for UAE are the "true" rate of these occurrences and that earlier studies have misled us as a result of incomplete or biased data reporting or study design flaws.

Is this the reality? What can we say about the study design of the EMMY Trial (1) and the relative merits that design might have? Clearly, the use of a randomized study design is preferred for any attempt to determine the relative effectiveness of two therapies and I applaud the efforts of the authors in completing this study. Attempts at completion of randomized studies in the United States have not succeeded to date, in most cases as a result of failure to recruit study participants.

Randomized design has the advantage of removing patient selection bias and it tends to yield comparable study groups (4). In addition, many statistical tests are based on the assumptions of random distribution of variables inherent in the randomization process. It is also true that patient reporting bias related to "buy-in" or preference for UAE over other therapies is eliminated in this study, as the patients in the EMMY Trial (1) were scheduled to undergo hysterectomy and therefore had no stated preference for UAE.

However, randomization addresses only the issues of patient selection and comparability of groups and is not the only criterion one should use in judging a study. There are a number of flaws in the EMMY Trial (1) that outweigh any strengths that might derive from its randomized design.

First, the power of this study to detect differences in short-term outcomes was not calculated. A very large number of variables were evaluated in a relatively small sample size and the likelihood of erroneous interpretation increases with each additional analysis.

Second, the patients included may have had a preference for hysterectomy, as they had already agreed to undergo that procedure. They may not have been enthusiastic about undergoing UAE or even had a bias against it, as they were recruited to this study by their gynecologists, who had little or no experience with the procedure.

Third, based on the information provided in the articles (1,2), the management plan for postprocedural pain, the manner of patient instruction, and follow-up of the patients treated with UAE do not meet the accepted practice standards at the time of the study. The patients were encouraged to take non-steroidal antiinflammatory drugs and paracetamol (acetaminophen). Only after the pain became severe were they given narcotics. The patients were not provided with routine in-hospital patient-controlled analgesia and apparently were not given any narcotics for use after discharge. There were no visits planned for 6 weeks after discharge and the only routine contact was a telephone call to the patient from the gynecologist 1 week after the procedure. The patients were told to call their gynecologists if their pain was not controlled. The radiologists had no role in caring for the patients.

This is a clear recipe for a poor outcome. Would any gynecologist accept the findings of a study in which patients had insufficient pain control after hysterectomy and the care was provided by radiologists? With the treatment plan in the EMMY Trial (1,2), there is no question that patients would commonly experience problems. With an appropriate regimen, pain after UAE is quite tolerable in most cases and reevaluation in the emergency room or readmission after embolization is rarely needed, as

found in the recent report of recovery after UAE (5). In that study, a group of 100 patients were followed prospectively and, in most cases, experienced only moderate pain in the first week after embolization (mean peak visual analog scale score of 4.9 on a 10-point scale). There was only one readmission for pain management. Successful management does not require a specialized center, just an appropriate pain management plan and careful patient instruction.

Finally, and perhaps most importantly, the operators in this study (1,2) were, for the most part, inexperienced with UAE and the gynecologists who provided all postprocedural care had essentially no experience with UAE. Of the 34 participating hospitals, 28 contributed patients, an average of three patients per hospital. For many of these centers, these were the first patients ever treated with UAE. This degree of inexperience may explain the very high rate of procedural failure on the part of the interventionalists. In addition, the gynecologists were ill equipped to manage these patients and yet were responsible for deciding whether patients required readmission and whether a patient's postprocedural problems represented a complication. Again, to use a gynecology analogy, this is the same as evaluating the outcome from hysterectomy by gynecologists performing their first several hysterectomies, with postoperative care managed by interventional radiologists with no experience in postoperative care.

It is true that these were experienced interventional radiologists in a range of other procedures, but every procedure has technical challenges and most would not want their skill judged by the first few procedures they performed. Even though the investigators analyzed the potential impact of experience on outcome, they compared those with less than 10 cases of experience to those with greater than 10 cases of experience. Ten cases is not a very high hurdle to be considered experienced, particularly in a trial intended to be a definitive evaluation of comparative outcomes. One would presume that the gynecologists had a greater level of experience performing hysterectomies than the interventionalists had with UAE.

How can one be sure that the find-

ings of the EMMY Trial (1,2) are not the true results that can be anticipated from embolization in general practice? Perhaps the best evidence comes from the recently published short-term fibroid registry results of Worthington-Kirsch et al (6). The registry included a total of 72 sites, with 26 core sites and 46 participating sites, with 30-day results in more than 2,700 patients. More than 300 of these patients came from sites with limited experience. In the registry, bilateral UAE was successful in 92.7% of patients overall, versus 82.7% in the EMMY Trial (1,2). The frequency of complications was also lower in the registry (6): 31.1% of patients had minor complications after discharge, versus 58% for UAE and 40% for hysterectomy in the EMMY Trial (1,2). The results from the registry (6) are drawn from a much broader range of practices than any other study to date and are the best

reflection of community practice we have.

What can we conclude? The results from the EMMY Trial (1,2) should not be taken as the definitive statement on early outcomes from UAE, regardless of its randomized design. Given the procedural failure rate of nearly 20% reported in these early results, we should also have concerns regarding its yet-unreported findings at 2 years. Although the effort of the EMMY Trial investigators to definitively answer important questions regarding outcomes of uterine leiomyoma therapies is admirable, we will have to await studies without its limitations to find those answers.

References

1. Volkers NA, Hehenkamp WJK, Birnie E, et al. Uterine artery embolization in the treatment of symptomatic uterine fibroid tumors (EMMY trial): periproce-
2. Hehenkamp WJ, Volkers N, Dondewinkel P, et al. Uterine artery embolization versus hysterectomy in the treatment of symptomatic uterine fibroids (EMMY trial): peri- and postprocedural results from a randomized controlled trial. *Am J Obstet Gynecol* 2005; 193:1618–1629.
3. Spies J, Cooper J, Worthington-Kirsch R, et al. Outcome from uterine embolization and hysterectomy for leiomyomas: results of a multi-center study. *Am J Obstet Gynecol* 2004; 191:22–31.
4. Friedman L, Furberg C, DeMets D. *Fundamentals of clinical trials*, 3rd ed. New York: Springer-Verlag, 1998.
5. Bruno J, Allison S, McCullough M, et al. Recovery after uterine artery embolization for leiomyomas: a detailed analysis of its duration and severity. *J Vasc Interv Radiol* 2004; 15:801–807.
6. Worthington-Kirsch R, Spies J, Myers E, et al. The Fibroid Registry for Outcomes Data (FIBROID) for uterine artery embolization: short term outcomes. *Obstet Gynecol* 2005; 106:52–59.