Pain after Uterine Artery Embolization for Leiomyomata: Can Its Severity be Predicted and Does Severity Predict Outcome?[1]

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Abbreviations: NRS = numerical rating scale, PCA = patient-controlled analgesia, UAE = uterine artery embolization, VAS = visual analog scale

PURPOSE: To determine whether the severity of postprocedure pain associated with uterine artery embolization (UAE) for leiomyomata can be predicted and if its severity can predict outcome.

MATERIALS AND METHODS: Eighty-one patients underwent UAE and had postprocedure pain managed with use of patient-controlled analgesia (PCA) in the form of an intravenous morphine pump. Baseline uterine and dominant fibroid volumes were calculated for each patient. Attempted doses, doses given, total morphine dose, and maximum numerical rating scale (NRS) score during postprocedure hospitalization were recorded. At 3 months postprocedure, repeat imaging was used to determine uterine and dominant fibroid volume reduction. Each patient also completed a questionnaire assessing change in menstrual bleeding, pelvic pain and pressure symptoms, and satisfaction with symptomatic outcome. Simple regression analysis was used to determine if baseline volumes predicted postprocedure pain and if the pain-related variables could be used to predict outcome.

RESULTS: Neither baseline uterine volume nor dominant fibroid volume predicted the severity of postprocedure pain. Similarly, none of the pain-related variables predicted uterine or fibroid volume reduction, symptomatic improvement, or satisfaction with outcome.

CONCLUSIONS: Postprocedural pain cannot be predicted based on baseline uterine or fibroid volume and the severity of pain experienced cannot be used to predict outcome.

UTERINE artery embolization (UAE) has been reported to be effective in treating symptomatic uterine leiomyomata (1–4). These studies suggest that UAE causes the degeneration and shrinkage of fibroids, controlling or substantially improving menorrhagia, pelvic pain, and pressure in more than 80% of patients. The magnetic resonance imaging (MRI) and pathologic findings reported suggest that the fibroids undergo hemorrhagic infarction and subsequent hyaline degeneration (5–7).

The infarction of the fibroids occurs in the first several hours after the embolization, causing considerable pain in many patients. Most physicians hospitalize their patients overnight for postprocedural pain control. However, a small percentage of women experience little or no pain in the hours after the procedure. One such patient at our center, who experienced no pain immediately after the procedure, also reported no resolution of symptoms at 3-month follow-up. MRI at that time demonstrated an increase in

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uterine and fibroid volumes, with no evidence of fibroid infarction. At her subsequent hysterectomy, extensive parasitized blood supply from other pelvic sidewall branches was identified. This abnormal blood supply is presumed to be the cause of the failure of the UAE procedure.

This case prompted us to investigate whether the severity of postprocedure pain correlates with identifiable preprocedure variables or postprocedure outcome. Is the patient who experiences little or no pain more likely to fail to respond to the treatment? Do patients with large fibroids experience more pain than those with smaller fibroids? Does an individual who has severe pain after UAE have more improvement in symptoms or a greater reduction in fibroid size than an individual who has little or no pain? Although Goodwin et al have commented that severe pain is not a predictor of outcome (4), there are no published data identifying factors that might predict pain severity or assess the relation of pain severity with outcome.

In this study, we attempted to determine whether the severity of pain a patient experiences after UAE for leiomyomata can be predicted before the procedure and whether the degree of pain experienced can be used to predict outcome.

MATERIALS AND METHODS

The study group included patients undergoing UAE at our institution between November 1998 and September 1999. Patients were included for analysis if complete records from their intravenous patient-controlled analgesia (PCA) pumps records were available.

During the study period, 102 patients were treated at our institution. Of these, 81 patients had complete PCA and numerical rating scale (NRS) data available and had undergone baseline MRI studies. This group comprised the study group. The PCA and NRS data were obtained and recorded prospectively for all patients. The analysis of that data began after 50 patients had been treated and their data were obtained from chart review after their discharge. The data were collected during hospitalization in 31 patients. The data were obtained by the nursing staff in the same manner for all patients.

Our patient population is comprised of self-referred and gynecologist-referred patients. Our protocol requires that each patient have symptoms caused by their fibroids, such as menorrhagia, pelvic or back pain, or pelvic or urinary pressure caused by the mass effect of their fibroids. Preprocedure evaluation included a history and physical examination, endometrial biopsy for patients with unusually prolonged or frequent bleeding (to exclude endometrial hyperplasia or carcinoma), and MRI. Volume measurements were recorded for the uterus and the largest fibroid (dominant) with use of the formula of a prolate ellipse (length $\times$ width $\times$ depth $\times$ 0.5233). A baseline symptom questionnaire was administered to assess patients' bleeding, pressure, pain, and urinary symptoms. The questionnaire asked patients to rate the severity of their symptoms on a rating scale from mild to severe. They were also asked to judge the impact of their symptoms on their daily life on a scale from 1 to 10.

Subsequently, each patient underwent bilateral UAE for their fibroids with use of 500–710 μm polyvinyl alcohol particles (Contour; Target Therapeutics/Boston Scientific, Natick, MA; Ivalon; Cook, Bloomington IN; Trufill; Cordis, Miami Lakes, FL). Embolization was continued until stasis or near stasis of uterine artery blood flow occurred. All patients remained in the hospital overnight for observation and pain control. Most patients experienced several hours of moderate to severe pain that was controlled with morphine sulfate (administered via a PCA pump) and ketorolac (Toradol; Roche, Nutley, NJ). The PCA pumps were started at the conclusion of the procedure in the angiography suite. Initial parameters for the PCA pump provided a 2-mg clinician bolus of morphine, a 1-mg demand dose with an 8-minute lockout period. There was no continuous infusion of morphine. Therefore, under the initial conditions, a patient might administer as many as 7 doses of 1 mg of morphine per hour. The orders allowed the nursing staff to increase the demand dose up to 2 mg or decrease it to 0.5 mg as needed. Additional clinician boluses or demand doses greater than 2 mg were ordered by the interventional staff if needed.

With use of an NRS from 0–10, with 0 representing no pain and 10 representing the worst imaginable pain (8), the nursing staff monitored patient pain every 2–4 hours. The highest score reported during the patient's overnight stay was used as an indicator of maximum postprocedure pain severity. The maximum NRS score, number of attempted PCA doses (the number of times a patient pushed the PCA button to obtain a dose), number of PCA doses administered, and the total amount of morphine was recorded. Clinician- and patient-administered doses were included in the total dose.

Each patient was discharged from the hospital after a 1-night stay in the hospital. After discharge, pain was controlled with oral ketorolac (Toradol; Roche) hydromorphone hydrochloride (Dilaudid; Knoll Laboratories, Mt. Olive, NJ), oxycodone and acetaminophen (Percocet; McNeil, Fort Washington, PA) and nausea was managed with promethazine HCl (Phenergan; Wyeth Ayerst, Philadelphia, PA). Only the intravenous narcotics given in the hospital were used in the pain analysis.

Questionnaires were sent at 3 months postprocedure. With use of an 11-point scale, the questionnaires were use to assess changes in bleeding, pain, and pressure symptoms and to determine the patient's overall satisfaction with the procedure. The scale ranged from -5 (markedly worse) to $+5$ (markedly improved), with 0 representing no change. For the purposes of this analysis, these responses were treated as continuous variables. Follow-up MRI was performed at 3

Table 1
Summary of Study Data

Item	Mean	SD	No. of Patients	Range
Attempted Doses	51.7	59.3	81	1–310
Doses Given	23.5	16.8	81	1–92
Total Dose	35	28	81	2–120
Maximum NRS Score	4.8	2.5	81	0–10
Baseline Uterine Volume (cm^3)	691.9	419.2	79	84–1961
Baseline Dominant Fibroid Volume (cm^3)	244.5	274.6	78	9–1351
Uterine Volume at 3 Months (cm^3)	481.2	341.9	71	73–1875
Dominant Fibroid Volume at 3 Months (cm^3)	146.1	115.7	71	1.2–1180
Uterine Volume Reduction at 3 Months (%)	.30	.21	71	−.12 to .91
Dominant Fibroid Volume Red. at 3 Months (%)	.40	.28	71	.9–99.6
Change in Bleeding at 3 mo.*	+3.3	2.0	73	−3 to +5
Change in Pelvic Pain/Pressure at 3 mo.*	+3.4	1.8	65	−3 to +5
Patient Satisfaction at 3 mo.†	+3.9	1.8	76	−5 to +5

* The scale is a balanced scale with 11 choices ranging from −5 for markedly worse to +5 for markedly improved, with 0 unchanged, +1 slightly improved, and +3 moderately improved.
† The scale is a balanced scale from −5 for very dissatisfied to +5 for very satisfied, with 0 neither satisfied nor dissatisfied, +1 slightly satisfied, and +3 moderately satisfied.

months and 1 year. Again, volume measurements of the uterus and the dominant fibroid were recorded.

Means and SDs for all the variables were calculated. A correlation matrix was used to determine if a relationship among the PCA-related variables could be detected.

Simple regression analysis was performed on all data. For the analyses of predictors of pain severity, the independent variables were dominant fibroid size and uterine volume, and the dependent variables were the NRS score, number of attempted doses of morphine, number of morphine doses received, and total morphine dose. For prediction of outcome, the independent variables were the NRS score, attempted doses, number of doses given, and total dose given. The dependent variables were symptomatic outcome scores and uterine and dominant fibroid volumes 3 months after UAE. The regression coefficient, F statistic, and *P* value are reported on all regression analyses. *P* values $<.05$ were considered statistically significant. All statistical results were computed with use of Statview Version 5.0 for Macintosh (SAS, Cary, NC).

RESULTS

The data on attempted doses (the number of times the patient pushed the button to receive a dose), doses delivered, total PCA dose, maximum NRS scales, baseline volumes, postprocedural volumes, volume reductions at 3 months postprocedure, and symptomatic outcome are summarized in **Table 1**.

Of the 81 patients, baseline uterine volumes were available for 79 and dominant fibroid measures were available for 78. Imaging at 3 months was available in 71. Follow-up questionnaires were obtained from 76 patients, 73 of whom originally had heavy bleeding and 65 of whom had pelvic pain and pressure.

There is wide variation among the PCA-related data. For example, the range of attempted doses ranged from 1 to 310, with a mean of 51.7 and a SD of 59.3. Similarly wide ranges and high SDs were noted with the other values. As expected, the number of doses attempted was much higher than the doses delivered. If a patient receives a dose and had received a dose in the preceding eight minutes, an attempt would be recorded but no dose would be delivered.

The correlation matrix for the PCA-related variables is given in **Table 2**. As might be expected, there is high correlation (0.86) between attempted doses and the number of doses given. There is moderate correlation between attempted doses and total dose and a moderate to strong correlation between number of doses given and total dose. There is only weak correlation between the maximum NRS score and the attempted doses, number of doses, and total dose.

The regression analysis revealed that baseline uterine volume and dominant fibroid volume did not predict any of the pain variables recorded. The results are given in **Table 3**. The regression coefficients (R^2) are very low, indicating that the outcome variables cannot be predicted on the basis of the independent variables. When expressed as a percentage, they indicate that baseline uterine and fibroid volumes explain no more than 3.5% of the pain variables. The *P* values are correspondingly high. Examples of the scatterplots of the results used in these analyses are given in the **Figure**.

At 3-month follow-up, 76 patients completed a symptomatic outcome questionnaire. From this subset, we attempted to predict improvements in bleeding, pressure, pain, and urinary symptoms from postprocedure pain scores with use of simple regression analysis.

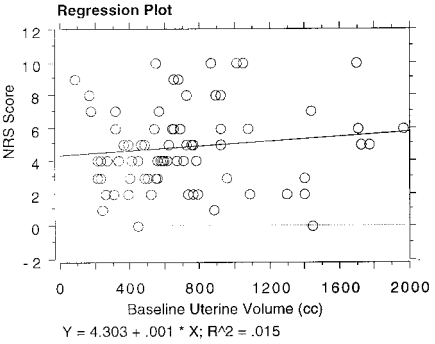
The results are summarized in **Table 4**. Again, the R^2 values are

Table 2
Correlation Matrix Assessing Relationship of Attempted Doses, Number of Doses Given, Total Dose, and NRS Score

	Attempted Doses	No. of Doses Given	Total Dose	NRS Score
Attempted doses	1.00	.86	.51	.16
No. of doses given	.86	1.00	.67	.18
Total dose	.51	.67	1.00	.17
NRS Score	.16	.18	.17	1.00

Table 3
Summary of Regression Analyses of Baseline Uterine and Dominant Fibroid Volumes in Predicting Total Morphine Dose and NRS

	R^2	f Value	*P* Value
Independent Variable: Baseline Uterine Volume			
Dependent Variable			
Attempted Doses	.035	2.8	.10
Doses Given	.032	2.58	.11
Total Morphine Dose	.010	.772	.38
NRS Score	.012	.939	.34
Independent Variable: Baseline Dominant Fibroid Volume			
Dependent Variable			
Attempted Doses	.029	2.24	.14
Doses Given	.013	1.04	.31
Total Morphine Dose	.010	.777	.38
NRS	.00016	.012	.9120



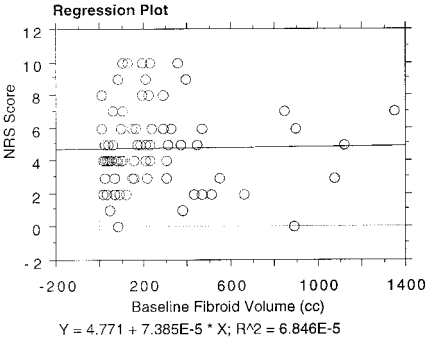


Figure. Examples of regression plots used in calculating regression data. The figure of at the top is a plot of maximum NRS score and baseline uterine volume. The figure at the bottom is a plot of maximum NRS score and baseline dominant fibroid volume.

very low, and none of the pain variables explains more than 3.6% of the outcome. All the *P* values are correspondingly high.

Three-month MRI data were available for 71 patients. These regression analyses, also given in **Table 4**, again showed that the volume reductions are not predicted by postprocedure pain.

DISCUSSION

Pain is a common side effect of UAE for leiomyomata (1–4). The specific etiology and implications of postembolization pain have not been identified with certainty, although the initial short-term severe pain is most likely the result of tissue ischemia. Pathologic and imaging evidence suggest that the fibroids undergo infarction as a result of embolization, leading to hyaline degeneration (6,7). As uterine embolization for leiomyomata becomes more commonly performed, understanding the management of postprocedure pain will be important. Before developing studies to compare various pain management strategies, we believe it is important to study patients that have been treated to determine if patterns or predictors of pain can be detected. We undertook the current study to begin this process.

The purpose of this study was two-fold. First, we attempted to determine whether the acute pain after UAE could be predicted based on baseline uterine and fibroid size. To select the best proxy for pain, we initially performed a correlation analysis to see if the four potential proxies for pain (attempted doses, doses given, total dose, and maximum score) correlated with each other. We were surprised that there was only a weak correlation between maximum NRS score and the other three parameters. This may reflect in part the limitation of PCA-administered analgesia. Despite careful instruction, patient use of PCA pumps varied greatly. Some patients apparently gave themselves frequent doses when there was little pain, which may have resulted in the perception of little pain (low NRS score) but high attempted doses, doses administered, and total dose. Conversely, if a patient chose to avoid use of medication, she might experience more pain but use relatively less medication. If a patient slept, she would not receive any medication but might awake with severe pain. In these situations, there may be a poor correlation among the variables. For this reason, we proceeded with regression analysis with use of

Table 4
Summary of Regression Analyses of Total Morphine Dose and NRS and Prediction of Volume Reduction and Symptomatic Outcome

Variable	R^2	f Value	*P* Value
Independent Variable: Attempted Doses			
Dependent Variable			
Uterine Volume Reduction	.012	.80	.37
Dominant Fibroid Volume Reduction	.007	.50	.48
Improvement in Menstrual Bleeding	.011	.81	.37
Improvement in Pelvic Pain and Pressure	.012	.76	.39
Satisfaction with Symptomatic Outcome	.001	1.1	.29
Independent Variable: Doses Given			
Dependent Variable			
Uterine Volume Reduction	.009	.60	.44
Dominant Fibroid Volume Reduction	.000032	.002	.96
Improvement in Menstrual Bleeding	.017	1.3	.27
Improvement in Pelvic Pain and Pressure	.005	.32	.57
Satisfaction with Symptomatic Outcome	.033	2.6	.11
Independent Variable: Total Dose			
Dependent Variable			
Uterine Volume Reduction	.015	1.07	.30
Dominant Fibroid Volume Reduction	.002	.147	.70
Improvement in Menstrual Bleeding	.036	2.67	.11
Improvement in Pelvic Pain and Pressure	.000018	.001	.97
Satisfaction with Symptomatic Outcome	.014	1.02	.32
Independent Variable: NRS Score			
Dependent Variable			
Uterine Volume Reduction	.009	.621	.43
Dominant Fibroid Volume Reduction	.031	2.20	.14
Improvement in Menstrual Bleeding	.002	.139	.71
Improvement in Pelvic Pain and Pressure	.006	.401	.53
Satisfaction with Symptomatic Outcome	.001	.099	.75

all the variables as potential dependent and independent variables.

Despite these multiple analyses, we found no relationship and no predictors of the severity of pain postprocedure. The NRS score, the total dose of morphine given via PCA pump, and the total numbers of attempted and administered doses could not be predicted based on the baseline size of the uterus or individual dominant fibroids. This reinforces our anecdotal experience that embolization of even the largest fibroids may cause little pain to some patients and conversely that infarction of small to medium-sized fibroids may cause severe pain.

If baseline uterine or fibroid volumes do not correlate to the acute pain caused by the procedure, can postprocedure pain severity be used to predict outcome? Again, our analysis did not detect any predictors of outcome. None of the parameters recorded during the postprocedure hospitalization correlated with the symptomatic outcome or fibroid or uterine volume reduction 3 months postprocedure. It is quite likely that other factors, such as the location of the fibroids within the uterus or the presence of adenomyosis, are more likely to predict symptomatic improvement. We do not know why there is such variability in the degree of shrinkage of fibroids after embolization, despite evidence of complete infarction on MRI. Possible explanations include the location of fibroids within the uterus, variable rates of degeneration of different pathologic subtypes of fibroids, or variability in individual patient inflammatory response.

These findings suggest that the severity of postprocedure pain cannot be predicted by baseline imaging and that the outcome cannot be predicted. This leaves unanswered the questions of why there is such variability in pain severity and narcotic requirement. We can speculate as to potential causes.

The first consideration is the scale used to measure acute pain. How accurately does it measure pain compared to other scales? In our study, the NRS was used to evaluate pain. This scale is somewhat different from the commonly used visual analog scale (VAS), which has been perhaps the standard for acute pain measurement since it was first popularized by Huskisson in the 1970s (9). There is, in fact, some confusion between the two scales. The VAS is a linear 10-cm scale with no interval gradations. One end is labeled "no pain" and the other is labeled "pain as bad as it could be" The patient is asked to mark a point along the continuum of the line which reflects the relative severity of her pain. The investigator then measures the distance in millimeters from the origin of the scale to the marked point, yielding a number that corresponds to the VAS score. Conversely, the NRS is a numeric scale from 0 (no pain) to 10 (worst imaginable pain). The patient is asked to pick a number from 0 to 10 that most closely corresponds to the degree of pain they are experiencing. The NRS is simpler to administer than the VAS, but the question arises as to the comparability of the scales.

Downie et al (8) evaluated the NRS and concluded that there is a high degree of correlation between it and the horizontal VAS. Specifically, initial evaluation of patient pain yielded a correlation between the two scales of 0.62, but repeated testing such as was used in our study yielded a correlation of 0.91. The NRS has advantages compared to other pain scales in terms of measurement error, and it is easier for patients to understand than the VAS is. It provides a good compromise between a four-point descriptive scale (mild, moderate, severe,

unbearable), which offers only a few choices, and the VAS, on which the greater freedom of choice may be confusing. We believe that we used an acceptable means of assessing the severity of pain.

One potential source of variability in the degree of pain that patients experience after embolization is in the cellular composition of leiomyomata. Variable amounts of smooth muscle and fibrous tissue are present in leiomyomata, which may affect ischemic pain. In addition, the innervation of fibroids may vary and this may, in part, relate to their position within the uterus. It is also possible that there is temporary global uterine ischemia contributing to the pain. All these possibilities are as yet unexplored.

Finally, it is well known that the narcotic dose needed to relieve pain caused by a given surgical procedure is extremely variable. For example, Tyler et al (10) reported on the variation of morphine use in adolescents after spinal surgery. In this study, morphine was administered via PCA pump. Morphine blood concentrations were measured and correlated well with morphine use, indicating that PCA doses can be used to approximate serum levels. Despite this finding, there was wide variation in morphine use, and neither the level of morphine use nor morphine concentration correlated with pain scores. The authors concluded that the variability of the dose used does not appear related to the metabolism of morphine, but is more likely to be related to psychologic differences, differences in pain tolerance and threshold, or differences in the way patients use PCA. We would agree: at our current level of knowledge, pain severity or analgesic use is subject to too much variability to be useful in guiding clinical decision making.

We acknowledge the limitations in our approach in this study. Our intent in this study was to determine which, if any, predictors could be identified that might allow us to modify preprocedure and acute postprocedure care to limit the degree of discomfort experienced by our patients. We realize that we might have used a more sophisticated approach to the analysis of the variables, including multiple regression. However, we sought to identify clinically useful predictors so they might be applicable in daily practice. If multiple regression had identified three or four variables that, in combination, would predict pain or outcome, it would have been too cumbersome for use in the management of individual patients. For this reason, we chose a simple regression analysis approach.

Although there are variables that we did not test, none of those we examined proved useful in guiding our care of patients. In light of this finding, we believe the next priority is to compare the various pain management programs that are available to determine those which are safest and most effective in improving the tolerability of this procedure.

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