Predictors and Outcomes of Crossover to Surgery from Physical Therapy for Meniscal Tear and Osteoarthritis

A Randomized Trial Comparing Physical Therapy and Surgery

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Background: Arthroscopic partial meniscectomy (APM) combined with physical therapy (PT) have yielded pain relief similar to that provided by PT alone in randomized trials of subjects with a degenerative meniscal tear. However, many patients randomized to PT received APM before assessment of the primary outcome. We sought to identify factors associated with crossing over to APM and to compare pain relief between patients who had crossed over to APM and those who had been randomized to APM.

Methods: We used data from the MeTeOR (Meniscal Tear in Osteoarthritis Research) Trial of APM with PT versus PT alone in subjects ≥45 years old who had mild-to-moderate osteoarthritis and a degenerative meniscal tear. We assessed independent predictors of crossover to APM among those randomized to PT. We also compared pain relief at 6 months among those randomized to PT who crossed over to APM, those who did not cross over, and those originally randomized to APM.

Results: One hundred and sixty-four subjects were randomized to and received APM and 177 were randomized to PT, of whom 48 (27%) crossed over to receive APM in the first 140 days after randomization. In multivariate analyses, factors associated with a higher likelihood of crossing over to APM among those who had originally been randomized to PT included a baseline Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain Score of ≥40 (risk ratio [RR] = 1.99; 95% confidence interval [CI] = 1.00, 3.93) and symptom duration of <1 year (RR = 1.74; 95% CI = 0.98, 3.08). Eighty-one percent of subjects who crossed over to APM and 82% of those randomized to APM had an improvement of ≥10 points in their pain score at 6 months, as did 73% of those who were randomized to and received only PT.

Conclusions: Subjects who crossed over to APM had presented with a shorter symptom duration and greater baseline pain than those who did not cross over from PT. Subjects who crossed over had rates of surgical success similar to those of the patients who had been randomized to surgery. Our findings also suggest that an initial course of rigorous PT prior to APM may not compromise surgical outcome.

Level of Evidence: Prognostic Level II. See Instructions for Authors for a complete description of levels of evidence.

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Degenerative meniscal tears are a common clinical problem that presents management challenges. Symptomatic, radiographically apparent knee osteoarthritis affects over 10 million adults in the U.S.[1], and up to 80% of individuals with knee osteoarthritis have imaging evidence of a meniscal tear[2]. More than 350,000 arthroscopic partial meniscectomies (APMs)

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TABLE I Proportion of Subjects Randomized to Nonoperative Therapy Who Crossed Over to Surgery and Proportion Randomized to Surgery Who Did Not Receive Surgery in Randomized Trials of Orthopaedic Surgical Interventions

Condition/Surgery	Duration of Follow-up *(yr)*	Crossover from Nonoperative to Surgery*	Randomized to Surgery but Failed to Receive Surgery†
Meniscal tear/APM			
Herrlin et al., 2013[5]	2	13/49, 27%	0/47, 0%
Katz et al., 2013[6] (>2-yr follow-up)	1	64/177, 36%	10/174, 6%
Yim et al., 2013[7]	2	1/54, 2%	0/54, 0%
Gauffin et al., 2014[4]	2	16/75, 21%	9/75, 12%
ACL tear/ACL reconstruction surgery: Frobell et al., 2010[24]	2	23/59, 39%	1/62, 2%
Lumbar spinal stenosis/standard posterior decompressive laminectomy			
Weinstein et al., 2010[22]	2	65/151, 43%	46/138, 33%
Delitto et al., 2015[21]	2	47/82, 57%	2/87, 2%
Lumbar degenerative spondylolisthesis/standard posterior decompressive laminectomy with or without fusion: Weinstein et al., 2009[23]	2	71/145, 49%	58/159, 36%
Lumbar disc herniation/surgery: Lurie et al., 2014[20]	2	110/256, 43%	104/245, 42%

*Number randomized to nonoperative treatment/number crossed over, percent crossed over. †Number randomized to surgery/number failed to receive surgery, percent failed to receive surgery.

are performed annually in the U.S., and thousands more are done worldwide, to treat meniscal tears presumed to be symptomatic in individuals with concomitant knee osteoarthritis[3].

The efficacy of APM in patients with osteoarthritis and a meniscal tear was examined in 4 recent randomized controlled trials that compared APM with a standardized physical therapy (PT) regimen. Three of the trials did not demonstrate a statistically significant or clinically important difference in symptomatic outcomes between subjects randomized to APM with PT and those randomized to PT alone[4-7]. One trial documented a statistically significant and clinically meaningful advantage for surgery[4]. However, these trials are difficult to interpret because up to one-third of subjects randomized to the PT arm crossed over and had APM before assessment of the primary outcome[4-6] (Table I).

The trial findings raise 2 questions that are the focus of this paper. First, what factors identify patients who are likely to cross over from nonoperative therapy to APM? If trial investigators could identify these patients, they might attempt interventions to reduce the likelihood of early crossover, since crossovers complicate the interpretation of randomized trials. There is little published information on predictors of crossover to surgery in this setting or, more generally, on predictors of the outcome of nonoperative therapy for a degenerative meniscal tear. Rimington et al. found that men with a degenerative meniscal tear were more likely to undergo surgical treatment compared with women with such a tear[8]. Additionally, smaller tears have been shown to do well with conservative treatment, with fewer people with such tears requiring surgical intervention[9].

Second, how successful is APM in relieving symptoms among patients who were randomized to PT and later crossed over to surgery as compared with patients originally randomized to APM? If those who crossed over to surgery did not do as well as those who had surgery at the outset, clinicians would be concerned that delay may compromise outcome. We address these questions using data from the MeTeOR (Meniscal Tear in Osteoarthritis Research) Trial.

Materials and Methods

Setting and Design

MeTeOR (ClinicalTrials.gov NCT00597012) is a 7-center randomized controlled trial of APM versus nonoperative therapy in subjects ≥45 years old with knee symptoms, a meniscal tear, and degenerative cartilage changes (including focal or diffuse cartilage defects) documented on radiographs and/or magnetic resonance imaging (MRI) studies. Subjects with Kellgren-Lawrence Grade-4 changes (>50% joint space narrowing) were excluded. Details of the study design, subject selection and enrollment, randomization, and outcome assessment have been reported previously[6,10]. Briefly, eligible subjects were randomized to receive either APM with a standardized PT regimen or the PT regimen alone without surgery. The details of the PT protocol was provided in Supplementary Materials attached to the original article on the trial[6], and enrollment and follow-up in the parent trial are shown in Figure 1 of that study and the present study. Of the eligible subjects, 26% agreed to enroll in the study and were randomized. Neither the subjects nor the surgeons were blinded to treatment assignment. The trial was powered to detect an 8-point difference in the primary outcome (Western Ontario and McMaster Universities Osteoarthritis Index [WOMAC] Pain Score[11]) at 6 months.

Baseline Variables

Baseline variables were ascertained prior to randomization with self-report questionnaires and with a physical examination performed by a trained research assistant. These variables included age, sex, body mass index (BMI), duration of symptoms prior to enrollment, preoperative level of pain and functional status (measured with the WOMAC[11] and Knee injury and Osteoarthritis Outcome Score [KOOS])[12], mechanical symptoms, mental health status (measured with the 5-item Mental Health Inventory[13]), Kellgren-Lawrence radiographic grade, and several physical examination variables including passive knee flexion and extension,

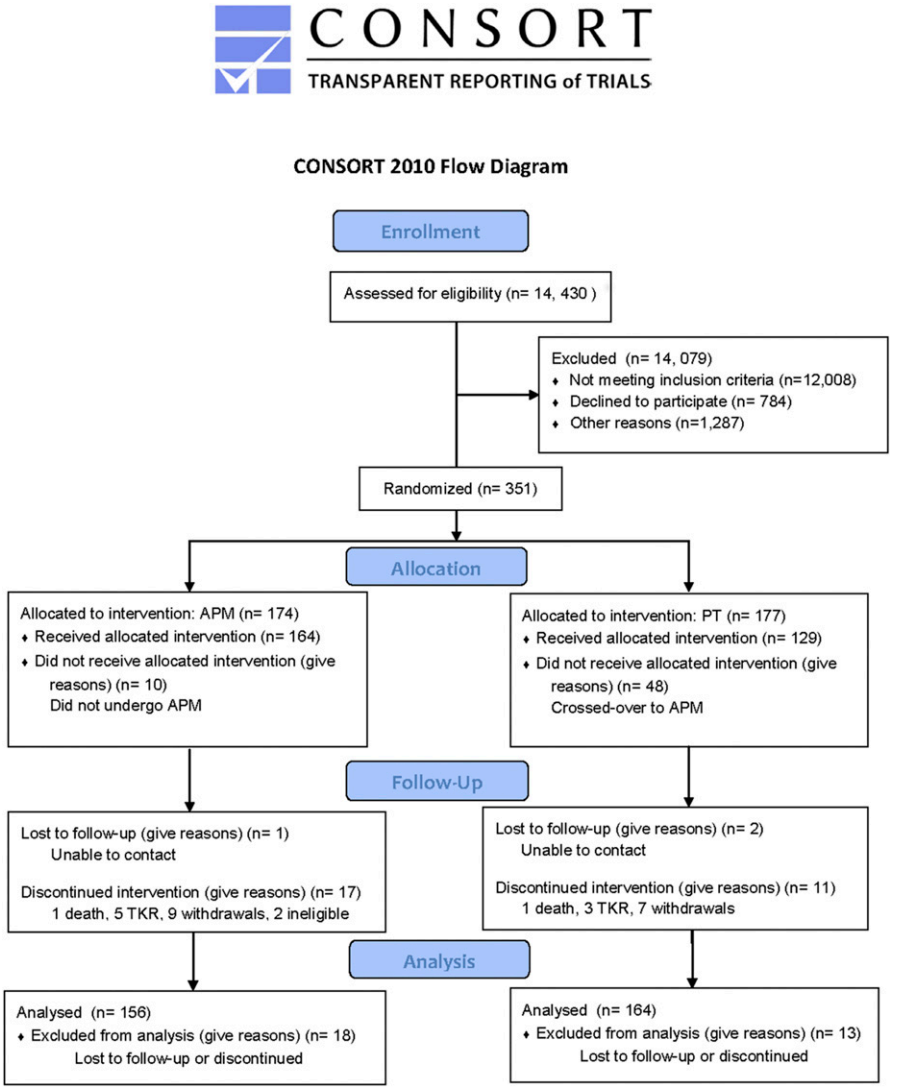

Fig. 1

Consort diagram for parent MeTeOR trial. TKR = total knee replacement.

strength (measured with a handheld goniometer), muscle lengths, static knee alignment, and the result of the timed "up and go" test[14-17].

Follow-up Protocol

Subjects completed questionnaires at the time of the 6-month follow-up after randomization. In this analysis, we examined baseline and 6-month data. We chose 6 months as the time to assess the primary outcome in order to capture the response to treatment, which is generally apparent at 6 months, while minimizing the potential for the pain score to reflect new problems in other lower-extremity joints or from another disease process in the index knee. The questionnaires included the WOMAC Pain and Function Scales and the KOOS Pain, Symptom, and Activity of Daily Living Scale. Study staff also called subjects every 2 weeks for the first 3 months after randomization to ascertain whether those assigned to surgery had undergone APM and whether those randomized to PT had crossed over and undergone APM.

Crossover Status

Subjects were permitted to see their orthopaedic surgeons throughout the study. If the subject and surgeon wished to proceed with surgery, the subject could cross over and undergo APM. At each follow-up call, study staff asked subjects whether they were continuing the original treatments or had crossed over to APM. Subjects were also asked about crossover each time that they completed a questionnaire. In these analyses, we included crossovers occurring in the first 140 days so that subjects would have at least 40 days to recover from surgery before the 6-month outcome assessment. Subjects randomized to surgery who did not ultimately undergo APM (6% of those randomized to surgery) were excluded from this analysis.

Statistical Analysis

We used generalized linear models with a binary outcome (crossover or not) to assess potential predictors of crossover to APM among those originally randomized to PT. We used a log link function to estimate risk ratios (RRs) rather than odds ratios (which take on more extreme values than RRs when used to assess a frequent outcome such as crossover). Potential predictors included duration of symptoms (dichotomized at 1 year), age, sex, BMI, preoperative level of pain and functional status, mechanical symptoms (as assessed with a 5-item inventory summed to a 0 to 100-point scale, in which 100 points is most severe, and dichotomized at 25 points), mental health status, Kellgren-Lawrence radiographic grade, and several physical examination variables as noted above. We considered variables with bivariate

TABLE II Factors Associated with Crossover from Nonoperative to Surgical Therapy in MeTeOR Trial

Factor	Crossover (No. [%])*		Risk Ratio (95% CI)	
	No	Yes	Bivariate Analysis	Multivariate Analysis
Sex			1.28 (0.78, 2.11)	
Male	49 (74%)	17 (26%)		
Female	63 (67%)	31 (33%)		
Age			1.18 (0.73, 1.91)	
<60 yr	74 (72%)	29 (28%)		
≥60 yr	38 (67%)	19 (33%)		
Baseline pain (WOMAC)			1.90 (1.05, 3.42)	1.99 (1.00, 3.93)
<40 points	46 (81%)	11 (19%)		
≥40 points	64 (63%)	37 (37%)		
Baseline function (WOMAC)			1.32 (0.79, 2.21)	
<37 points	51 (74%)	18 (26%)		
≥37 points	44 (66%)	23 (34%)		
Mechanical symptoms (on 0 to 100-point scale)			1.20 (0.72, 1.99)	
<25 points	56 (68%)	26 (32%)		
≥25 points	50 (74%)	18 (26%)		
BMI			1.16 (0.68, 1.96)	
<30 kg/m^2	52 (67%)	26 (33%)		
≥30 kg/m^2	37 (71%)	15 (29%)		
Symptom duration			1.65 (0.97, 2.83)	1.74 (0.98, 3.08)
<1 yr	48 (77%)	14 (23%)		
≥1 yr	52 (63%)	31 (37%)		
No. of comorbidities			1.00 (0.82, 1.23)	
0-1	60 (71%)	25 (29%)		
≥2	52 (70%)	22 (30%)		
Kellgren-Lawrence grade			1.03 (0.55, 1.95)	
<3	74 (72%)	29 (28%)		
3	24 (73%)	9 (27%)		
Mental Health Index-5 item			1.03 (0.64, 1.67)	
<85 points	56 (71%)	23 (29%)		
≥85 points	56 (70%)	24 (30%)		
Index foot planus			1.45 (0.87, 2.43)	
No	85 (74%)	30 (26%)		
Yes	23 (62%)	14 (38%)		
Knee flexion			1.32 (0.81, 2.14)	
<120°	35 (65%)	19 (35%)		
≥120°	74 (73%)	27 (27%)		
Flexion contracture			1.69 (0.83, 3.44)	
<3°	80 (67%)	39 (33%)		
≥3°	29 (81%)	7 (19%)		
Hamstring strength			1.80 (0.97, 3.34)	
<30 lb (<13.6 kg)	42 (81%)	10 (19%)		
≥30 lb (≥13.6 kg)	66 (65%)	35 (35%)		
Swelling			1.59 (0.78, 3.23)	
No	27 (79%)	7 (21%)		
Yes	82 (67%)	40 (33%)		

*Totals across cells differ for the different factors because of missing data.

associations with crossover at $p < 0.20$ for inclusion in the multivariate model. We then manually eliminated variables that did not contribute meaningfully to arrive at a parsimonious model. We also compared the likelihood of achieving a ≥10-point improvement in the KOOS Pain Score (considered a clinically important improvement[18]) between those randomized to PT who crossed over to APM and those originally randomized to APM. Finally, to complement the analysis of the binary primary outcome—achieving a ≥10-point improvement—we also examined the difference between these 2 groups regarding the absolute improvement in the KOOS Pain Score (a continuous outcome).

Results

Features of Study Sample

Of the 351 subjects enrolled in the MeTeOR Trial, 174 were randomized to APM, of whom 164 received surgery, generally within 3 weeks after randomization. One hundred and seventy-seven were randomized to PT, of whom 48 (27%) crossed over to receive APM in the first 140 days after randomization. Another 16 crossed over between 140 days and 24 months. Of those randomized to PT, 59% were female and 64% were <60 years old; 76% had Kellgren-Lawrence Grade-0, 1, or 2 radiographic changes and 24% had Grade 3. Sixty-four percent of the subjects randomized to PT had a WOMAC Pain Score of ≥40 at baseline (on a scale of 0 to 100), indicating a moderately high level of knee pain.

Factors Associated with Crossover (Table II)

The data did not provide evidence that demographic factors, including age, sex, and BMI, were associated with crossing over to surgery among patients randomized to PT. Similarly, we did not observe evidence that meniscal symptoms (either aggregated or separated as intermittent locking or catching), medical comorbidities, or mental health were associated with crossover from PT to APM. Several physical examination factors, including varus and valgus knee alignment and quadriceps and hamstring muscle lengths, were also not associated with crossover status. In the bivariate analyses, a duration of symptoms of <1 year was associated with crossover (RR = 1.65; 95% confidence interval [CI] = 0.97, 2.83), as was a baseline WOMAC Pain Score of ≥40 (RR = 1.90; 95% CI = 1.05, 3.42). Subjects with hamstring strength of <30 lb (13.6 kg) (RR = 1.80; 95% CI = 0.97, 3.34), those with normal knee extension (RR = 1.69; 95% CI = 0.83, 3.44), and those with swelling (RR = 1.59; 95% CI = 0.78, 3.23) were also somewhat more likely to cross over to APM, although the associations did not reach significance.

In multivariate analyses, factors associated with a higher likelihood of crossing over to APM among those randomized to PT included a baseline WOMAC Pain Score of ≥40 (RR = 1.99; 95% CI = 1.00, 3.93) and a symptom duration of <1 year (RR = 1.74; 95% CI = 0.98, 3.08). With these variables included in the model, none of the other factors (e.g., hamstring strength, knee extension, or swelling) made a significant contribution.

We performed sensitivity analyses to examine the effects of different specifications of potential predictors of crossover. For example, we dichotomized the Kellgren-Lawrence grade at 0 and 1 versus 2 and 3. The newly dichotomized variable was not associated with crossover (RR = 1.29; 95% CI = 0.75, 2.20, for Grades 0 and 1 versus 2 and 3).

Association Between Crossover Status and Outcome of Surgery

The proportion of subjects who achieved a ≥10-point improvement in KOOS Pain Score was 82% in the group randomized to APM, 73% in the group randomized to PT who did not later cross over to APM, and 81% of the subjects who crossed over to APM. In multivariate analyses, those who crossed over to APM had a virtually identical likelihood of achieving a ≥10-point improvement in the KOOS Pain Score as subjects originally randomized to APM (RR = 0.95; 95% CI = 0.64, 1.41), after adjustment for baseline pain and duration of symptoms. The 2 groups also had similar absolute improvements in the KOOS Pain Score over 6 months. Subjects randomized to APM had an average improvement of 24.5 points (standard error [SE] = 1.5 points) and those randomized to PT who crossed over to APM had an average improvement of 27.1 points (SE = 2.8 points); the difference between the 2 groups averaged 2.7 points (SE = 3.2 points; $p = 0.41$).

Discussion

In this study, we examined factors associated with crossover from PT to APM and we compared the outcome, in terms of relief of symptoms, of APM between subjects randomized to APM and those who crossed over from PT to APM. The findings suggest that patients assigned to PT who are most likely to cross over to APM are those with a more acute and painful presentation, characterized by a short duration of symptoms and higher pain scores. The findings also suggest that patients who cross over to APM are as likely to experience improvement in pain scores as those originally randomized to APM.

In several trials comparing APM and nonoperative therapy for subjects with knee pain, a meniscal tear, and osteoarthritis, up to one-third of the patients assigned to nonoperative therapy crossed over to receive APM over the course of follow-up[4-6] (Table I). These crossovers complicate interpretation of these trials, as subjects analyzed in the nonoperative arm actually underwent the surgical intervention but had to be included in the group to which they had been randomized in an intention-to-treat analysis. Substantial crossover from nonoperative to operative therapy has also been reported in trials of total knee replacement versus PT[19]; spine surgery versus usual care for lumbar disc protrusion[20], lumbar spinal stenosis[21,22], and degenerative spondylolisthesis[23]; and treatment of anterior cruciate ligament (ACL) tears[24] (Table I). The authors of several prior trials comparing surgery and nonoperative therapy examined factors associated with crossover from nonoperative to surgical arms. Delitto et al. showed that lower educational status and greater baseline pain were associated with a higher risk of crossover in their trial comparing surgery and PT for lumbar spinal stenosis[21]. The SPORT (Spine Patient Outcomes Research Trial) investigators reported that subjects who crossed over from nonoperative therapy to surgery in a trial of surgery for lumbar disc protrusion, spinal stenosis, and degenerative spondylolisthesis had been more bothered by their symptoms and had expressed a greater preference for surgery at baseline compared with those who did not cross over[23,25,26]. Rimington et al. found that men with a degenerative meniscal tear were

more likely than women with such a tear to undergo surgical treatment[8]. Also, smaller tears appear to be associated with greater success of conservative treatment[9].

Our finding that subjects with greater pain at baseline were more likely to cross over to surgery is consistent with the prior findings described above. On the question of whether subjects who cross over to APM have outcomes similar to those of individuals originally randomized to surgery, our findings mirror those of Herrlin et al., who noted that the 13 patients who crossed over from their PT arm to their APM group had the same levels of improvement at the 6-month follow-up evaluation as those who had been randomized to APM[5]. Delitto et al. also noted that subjects randomized to decompressive surgery for spinal stenosis and those randomized to nonoperative therapy who later crossed over to surgery had similar outcomes[21].

Several limitations of our study should be noted. In the MeTeOR Trial, only 26% of eligible subjects chose to participate, potentially limiting external validity[6]. Furthermore, the sample size was modest, with 48 subjects experiencing the outcome of interest—crossover to APM in the first 140 days after randomization to PT. In addition, because subjects were not randomized to either cross over or not cross over, our comparison of surgical results between those randomized to surgery and those who crossed over from PT to surgery is vulnerable to confounding. We addressed this issue with multivariate analysis and noted that the nearly identical outcomes between those randomized to APM and those who crossed over to APM persisted after adjustment with the factors available to us. We were not able to use MRI measures, activity level, or meniscal tear type as predictors of crossover, and we did not have objective measures of outcome. We also did not have information regarding patient preferences for surgery at baseline enrollment.

The strengths of this study include the prospective design, multicenter setting, and extensive array of baseline questionnaire and physical examination data.

These findings have implications for research and practice. From a research standpoint, crossovers complicate interpretation of clinical trials. Our findings suggest that crossovers are difficult to predict, as reflected by the modest risk ratios associated with the risk factors that we identified. However, the factors that we identified point toward a combination of characteristics placing a subject at risk for crossover: severe pain and a relatively short symptom duration. Investigators may wish to make special efforts to keep these subjects in nonoperative therapy. As indicated above, prior research has also documented higher crossover rates for subjects with greater baseline pain[22,23,25,26]. From a clinical standpoint, our data suggest that the outcome of surgery is probably similar between patients who undergo surgery earlier and those who do so after crossing over from PT. These findings underscore the emerging treatment recommendation in this clinical setting to try a PT regimen before opting for APM[27]. Finally, the similarity of the outcomes among subjects randomized to APM, those who crossed over to APM from PT, and those randomized to PT who did not cross over underscores the important role that patient preferences should play as patients and their clinicians discuss treatments for degenerative meniscal tears. ■

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