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A Randomized Trial of Realignment Therapy for Treatment of Medial Tibiofemoral Osteoarthritis

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Abstract (Word Count 298)
Objectives: The objective of this 30-week randomized crossover trial was to determine whether a multi-modal realignment therapy would be successful in relieving pain and improving function among persons with medial tibiofemoral OA.
METHODS: We conducted a double blind, *randomized crossover trial* of a multi-modal realignment therapy for persons with medial tibiofemoral OA. Trial participants met ACR criteria for OA with knee pain, aching or stiffness on most days of the past month and radiographic evidence of a definite osteophyte with predominant medial tibiofemoral OA. We tested two different treatments: A) CONTROL TREATMENT consisting of a neutral knee brace (no valgus angulation), flat unsupportive foot orthoses, and shoes with a flexible midsole; and B) ACTIVE TREATMENT consisting of a valgus knee brace, customized neutral foot orthoses, and shoes designed for motion control. For each subject, the *trial lasted 30 weeks*, including 12 weeks each of active and control treatment separated by a 6-week washout period. The primary outcome of the linear regression model was change in knee pain and function as assessed by the WOMAC Osteoarthritis Index.
RESULTS: 80 participants with medial tibiofemoral OA were randomized. Their mean age was 62 years, mean BMI was 34 kg/m^2 and mean WOMAC pain score was 9.2 (0-20 scale). There was no evidence of a carryover effect. The regression model demonstrated that the mean difference in pain between the active and control treatments was -1.82 units (95% confidence interval: -3.05 to -0.60 [*p*=0.004]) on the WOMAC pain scale, indicating a small, but statistically significant decrease in pain with the multi-modal active treatment. For WOMAC function the realignment intervention had a non-significant effect on function with a -2.90 unit decrease (95% CI -6.60 to 0.79) compared with the control condition (p=0.12).
CONCLUSION: Multi-modal realignment therapy decreases pain in persons with medial tibiofemoral OA.

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Introduction

The etiopathogenesis and progression of symptomatic knee osteoarthritis (OA) is driven by mechanical factors [1]. A number of biomechanical studies have demonstrated improvements in certain aspects of gait and biomechanics with valgus bracing among persons with knee osteoarthritis (OA) [2-4]. In addition, numerous randomized controlled trials (RCT) have investigated the clinical effects of valgus bracing in improving pain and function outcomes among persons with symptomatic knee OA [3;5-15]. While the findings have generally been supportive, several study design limitations, including the studies being uncontrolled [5-10] and/or underpowered [11-15], have called the results of these few RCTs into question [16;17].

The two largest studies to date have suggested positive effects on symptoms. Kirkley et al [18] found significant improvements in the braced treatment group compared with an unbraced control group. However, this trial may not have been appropriately controlled since an active brace intervention was compared to no intervention at all [18]. Given the profound effects of placebo in OA [19], and the potential for symptomatic improvements with neoprene sleeve interventions alone [20], the findings of the Kirkley trial require confirmation. A more recent RCT by Brouwer et al [21] found that valgus knee bracing resulted in improved knee function but no significant improvements in knee pain compared with no bracing. However, many participants in the Brouwer trial did not fully adhere to brace treatment as a result of skin irritation and poor fit.

Given the findings of previous trials have been somewhat equivocal, disease management guidelines have not advocated for the use of braces and have recommended further research is needed [17]. Echoing this need, recent systematic reviews of unloader braces for knee OA found modest evidence for their effectiveness and also recommended that further research be conducted [3;16]. Hence the need for an appropriately powered and well-controlled trial of the effect of valgus knee bracing among persons with medial knee OA.

Unfortunately, biomechanical studies demonstrate that even with appropriate valgus bracing, large mechanical stresses on the knee can persist, suggesting that the addition of other interventions to further improve limb alignment may be of therapeutic value [9]. Multiple orthotic modalities to decrease forces across a knee may be necessary in order to fully unload an osteoarthritic medial compartment and bring about significant improvements in knee pain and function. Recognizing the relationship between knee and foot biomechanics [22], the combination of a valgus knee brace with motion-control shoes and neutral foot orthoses has been proposed as a promising multi-modal strategy [3].

The overall objective of this study was to determine whether, among patients with medial tibiofemoral OA, the provision of a multi-modal realignment therapy relieves knee pain and improves function in a **30-week randomized crossover clinical trial**. We tested the hypothesis that, compared to control treatment, a multi-modal ***realignment therapy that includes a valgus knee brace, motion control shoes, and neutral foot orthoses (customized shoe inserts)*** is effective in reducing pain and improving function among persons with medial tibiofemoral OA.

Materials and Methods

Design Overview

This study was a double blind (participant and assessor), ***randomized crossover trial*** of a realignment therapy for patients with medial tibiofemoral osteoarthritis with the primary outcome being knee pain and function as assessed by the WOMAC Osteoarthritis Index (VAS Version) [23]. The trial was prospectively registered with the NIH Clinical Trials Registry NCT00124462 and approval was given by the Boston University IRB and the New England Baptist Hospital IRB. All participants provided written informed consent. The study conformed to the CONSORT requirements for RCTs. Study design and protocol development began in January 2005. Recruitment and enrolment began in June 2005. Follow-up of all subjects was completed in September 2008.

Given the possibility that even braces with no realigning capabilities can provide sensory input and improve symptoms on that basis alone, we compared the effects of the active brace treatment to the effects of a control treatment consisting of comparable braces without realigning capabilities:

1. CONTROL TREATMENT (A): A neutral knee brace that does not have any varus/valgus angulation was given along with flat, unsupportive foot orthoses and shoes with a flexible midsole.

2. ACTIVE TREATMENT (B): A valgus knee brace was given with customized neutral foot orthoses and motion control shoes.

A run-in design was used in order to maximize the likelihood of recruiting subjects who would remain in the trial. Subjects were randomized to receive either brace treatment A or brace treatment B for the initial 12 weeks. After 12 weeks, we removed the assigned brace, and participants received no therapy for 6 weeks. Following this 6-week wash-out period, the

alternative brace treatment was assigned for the final 12 weeks. For each subject, the ***trial lasted a total of 30 weeks***.

Intervention (Figure 1)

The active treatment consisted of a DonJoy OAdjuster knee brace (DonJoy Braces, Inc., Coconut Creek, FL) with bilateral customized semi-rigid functional foot orthoses which were crafted according to methods previously described [24] using heat-moldable Fastech (Fastech Labs, Inc., Troy, MI) shells and medium density Nickleplast-S (Alimed, Inc., Dedham, MA) inners to support a neutral foot position. The custom made foot orthoses replaced the normal insoles of a New Balance 830 motion control shoe (New Balance, Inc., Brighton, MA). The control brace consisted of the DonJoy Montana brace with a loosened screw at the hinge allowing varus-valgus laxity, a flat unmolded 1/16" FastTech Orthotic Blank of an identical material (Poron) to the active treatment but without the heat moldable core, and a New Balance court shoe (model 505) with a low density midsole and flexible upper to minimize motion control. Shoes and orthoses were worn on both feet during each treatment period.

Eligibility Criteria:

Trial participants met ACR criteria for osteoarthritis with knee pain, aching or stiffness on most of the past 30 days and evidence on radiograph of a definite osteophyte. In addition, because we were interested in ***persons with predominantly medial tibiofemoral osteoarthritis***, participants had radiographic evidence of disease in the medial tibiofemoral compartment without predominant lateral tibiofemoral or patellofemoral involvement. Medial tibiofemoral disease [25] required definite radiographic OA with at least grade 1 medial joint space narrowing (0-3 scale) using the Osteoarthritis Research Society International (OARSI) atlas [26]. Individuals with clinical evidence of patellofemoral disease or knee pathology (other than medial compartment OA) that was likely to be contributing to their knee pain (such as pes anserine bursitis) were excluded. Participants had to be ambulatory and limited in usual activities due to knee pain. The anatomic axis was measured from the short films using previously validated methods [27].

Exclusion criteria included: 1) Individuals who usually used an ambulation aid to walk, such as a cane, crutch, walker or wheelchair; 2) Amputation of a foot or previous major trauma to a foot that would raise concerns about whether an orthosis might worsen foot pain; 3) Known neuropathy due to diabetes or other causes; 4) Past history of deep vein thrombosis; 5) Pain emanating more from the back or hip than from knee as determined by a screening questionnaire and clinic exam; 6) Planning to move from the area within 9 months of study

screening; 7) Symptomatic comorbid disease that limits walking more than knee pain; 8) Receiving corticosteriod injections in the knee in the month prior to starting the trial; 9) For participants on glucosamine and/or chondroitin and/or NSAID, we required that they must be on a stable dose for at least 2 months prior to beginning the trial and commit to not starting any new treatments during the trial; 10) Bilateral total knee replacements (TKR) or plan for TKR of the index knee in next 6 months; 11) Other known causes of arthritis including rheumatoid arthritis, SLE, gout, psoriatic arthritis, and pseudogout; or 12) Failure to pass the 2 week run-in test; 13) Height of 5'0" or less due to incompatibility with brace fitting; 14) Past use of prescription brace or custom orthotic.

Additionally persons with low WOMAC pain scores at the time of pre-randomization screening were excluded. In order to properly evaluate response to treatment, we required that patients have a minimal score of at least 2 out of 5 on at least 2 of the 5 WOMAC questions, or a total of greater than 6 out of 20 on the WOMAC pain scale in the index knee during both a pre-randomization phone call and a screening visit. In the event that both knees met all eligibility criteria, the most symptomatic knee served as the index knee.

Recruitment

Participants were recruited using various forms of advertising in local public media, from among patients in the rheumatology and orthopedic sections of Boston Medical Center and New England Baptist Hospital, and from persons already recruited for other clinical trials.

The efficacy of a clinical trial is maximized if subjects comply with assigned treatment and come to scheduled visits. One way to increase the likelihood of subject compliance with a trial is to perform a ***run-in test***, a period of observation prior to randomization during which subjects get experience with major components of the study protocol. Those subjects who have trouble complying with the protocol are excluded before being randomized. Participants had a 2-week ***placebo run-in*** [28] with administration of the control shoe and control foot orthosis. Blindness was re-assessed at the beginning of the study and equal numbers of participants considered the control shoe and orthosis active and placebo interventions respectively.

We preserved allocation concealment by having the randomization codes held by a biostatistician at the Boston University School of Public Health, which is external to the Clinical Epidemiology and Research Training Unit where the trial examiners were located. We stratified patients into those with end stage (Kellgren & Lawrence Grade 4) OA and those with disease that was mild or moderate yet still predominantly affecting the medial joint. We then performed

computer generated blocked stratified randomization in order to ensure that roughly equal numbers of patients with severe and mild / moderate disease were randomized into each of the two treatment arms. The enrolment of participants and their assignation to intervention were conducted by separate research coordinators.

Blinding

Participants were told only that we were comparing two types of treatment for their knee arthritis. We did not specify which therapy constituted active treatment. A single blinded examiner administered the knee pain and function outcome measures, while a second investigator with experience in foot orthotic customization (KDG) fitted the shoe and customized the foot orthoses.

Adherence

We applied a number of different methods to monitor and improve adherence. Educational messages on the potential benefits of non-pharmacologic therapy and skills training on donning the alignment therapies were discussed and provided to participants to increase confidence and motivation to comply [29-31]. We inquired in a detailed fashion into adherence during each visit. To assess adherence, we called the subjects every week during the active phases of the trial (Phase 1: 0-12 weeks (visits occurred at 0, 1, 3, 6 and 12 weeks); and Phase 2: 18-30 weeks (visits occurred at 18, 19, 21, 24 and 30 weeks)). In addition, subjects kept a diary recording their daily use of the combination of brace, shoes and insert during the course of the trial, and a pamphlet was issued which addressed common concerns that might interfere with adherence. Participants were encouraged to wear the interventions for a minimum of 4 hours per day.

Study Outcomes

The primary outcomes were the WOMAC Pain and Function Subscales [23]. The WOMAC, which has been extensively validated and is recommended by the OARSI for use in OA clinical trials, has three subscales: the pain (5 items) subscale, the stiffness (2 items) subscale, and the physical function (17 items) subscale. In this study, results on the pain and physical function subscales were analyzed separately. All of the subscales have high test-retest reliability, and validation studies have shown high correlations with other indices probing similar constructs [23]. In terms of responsiveness to change, the WOMAC has been compared to other measures of patient status in OA including the Doyle index, the Lequesne index, walk time and range of motion [32-35] and has generally been found to be more responsive than these other instruments.

Statistical Analysis

Analysis of this trial focused on the primary outcome measure, which was change in WOMAC pain during treatment. The primary study question was whether the change in pain during the active treatment period differed from the change in pain during the control treatment period. We made similar comparisons of changes in WOMAC function scores during the active and control treatment periods.

We performed regression analysis of the relationship between treatment type (active or control) and WOMAC pain and function scores during the treatment period. We used a GEE (Generalized Estimating Equations) correction to account for repeated measures within individual participants. These methods were similar to those used in a prior crossover trial in OA [36]. Additional regression models were constructed using an interaction term of treatment by period as predictors. In a two-period crossover trial, the treatment by period interaction is equivalent to the carryover effect, so this provided a method of assessing carryover effect. The washout period of six weeks between treatment periods was intended to reduce the likelihood of a carryover effect. This analysis used an intent-to-treat approach with the last observation brought forward for missing values.

All statistical analyses were performed using version 9 of the SAS statistical analysis software package. The GENMOD procedure was used for regression analyses with GEE corrections for repeated measures.

Statistical power estimates: Based on the results from the Horlick [15] and Kirkley [18] trials of valgus knee bracing, we anticipated a conservative treatment effect difference of 30% in pain and function. We estimated a correlation of 0.6 in the primary outcome measure (WOMAC pain) for measures taken within a subject. With 80 participants, we had 80% power (with an alpha of 0.05 in a 2-sided test) to detect a treatment effect of 30% reduction of WOMAC pain compared with the control condition.

Results

Of the 860 potential participants who were contacted by phone, 229 were eligible for a screening visit. The most common reason for ineligibility was insufficient pain. Of the 150 participants who had a screening visit, 80 were found to be eligible and were randomized. Of the 80 participants enrolled, 56 completed the study (Figure 2). The main reasons for early termination were loss to follow-up, non-compliance, and scheduled joint replacement.

There were no statistically significant differences in age, gender, BMI, or radiographic severity between those who were randomly assigned to receive the active treatment first and those who were randomly assigned to receive the control treatment first (Table 1). Baseline WOMAC pain score was slightly higher in the group randomized to the active treatment first.

When analyzing the crossover trial findings for pain, we first tested for treatment period and differential carryover effects (Table 2 and Figure 3). The treatment period effect was a 0.43 unit difference (p = 0.66) in WOMAC pain change score, and the differential carryover effect was only a -0.10 point difference in the WOMAC pain change score (p = 0.95), indicating that treatment effectiveness did not depend on whether a participant was randomized to the active or control treatments first. Therefore, we removed the carryover term from the model. In Model 2, excluding the differential carryover effect, the realignment intervention had a significant effect on pain with a -1.82 unit decrease in pain (95% CI -3.05 to -0.6) compared with the control condition (p = 0.004).

For WOMAC function, the treatment-period effect was a 0.58unit difference (p = 0.84) (Table 3 and Figure 4), and the differential carryover was a 0.99 unit difference on the 68-unit WOMAC function scale (p= 0.82), indicating once again that treatment effectiveness did not depend on whether a participant was randomized to the active or control treatments first. Therefore, we removed the carryover term from the model. In Model 2, excluding the differential carryover effect, the realignment intervention had a non-significant effect on function with a -2.90 unit decrease (95% CI -6.60 to 0.79) compared with the control condition (p=0.12).

To facilitate understanding of the phase specific effects (consistent with Figures 3 and 4) we have inserted additional information about pain and function by phase (Table 4). This incorporates the carryover effect test and the estimated treatment effect from model 2(without carryover effect) from Tables 2 and 3. The results are consistent with a favorable effect for realignment compared to placebo in each treatment phase.

The adherence of study participants and reported side effects are detailed in Table 5. On average, participants wore the interventions for more than 3 hours per day. The most frequent side effect reported among persons wearing the realignment therapy compared to the control was problems with brace positioning or slipping (16 participants compared to 4 in the placebo group). Participants also more frequently reported pain from poorly fitting shoes during the active treatment period (7 participants compared to 1 during the control period).

Discussion

The need to develop efficacious, conservative, non-pharmacologic treatment approaches that are capable of ameliorating the symptoms of people with knee OA is an important research objective [37]. Despite insufficient attention from researchers and clinicians, therapies capable of targeting the pathomechanics of OA are likely to be efficacious [38]. We have demonstrated that the application of realignment therapy consisting of a DonJoy OAdjuster knee brace, customized foot orthoses, and New Balance 830 motion control shoes leads to a statistically significant improvement in knee pain compared to a placebo intervention.

The direction of effect (a 1.8 unit reduction in WOMAC pain) is consistent with the positive effects seen in other randomized trials of knee braces [15;18;21]. However, the magnitude of effect (~20% reduction in pain from baseline) is slightly less than that seen in previous brace trials. This discrepancy may result from differences in study design and the particular interventions tested. First, our study intervention involved not just a brace but also a motion control shoe and a foot orthosis. Two previous trials demonstrated that wearing a valgus knee brace alone can result in substantial improvements in the pain and function of patients with medial knee OA [15;18]. However, in contrast to these two previous trials, we also employed a rigorous control intervention, making demonstration of a sizable treatment effect more challenging. A third trial by Brouwer et al [21] failed to demonstrate the efficacy of unloader bracing (either varus or valgus) within a study sample that included persons with both lateral and medial tibiofemoral OA. Among the possible reasons for failure to demonstrate treatment efficacy in the Brouwer trial were problems with adherence to brace treatment, mainly because of skin irritation and poor fit. Subgroup analysis of persons with medial knee OA did find significant improvements in function among persons who were braced. In addition we have conducted a placebo controlled trial where the control group received similar intervention and equal attention as the intervention group. Hence, what we have is the specific treatment effect distinct from the placebo effect. The placebo effects for self-reported outcomes such as pain and function in OA trials is substantial [39]. This is a challenging aspect of trials particularly of non-pharmacologic treatments such as this trial [40].

The medial compartment of the knee absorbs 60-70% of the force across the joint during weight bearing [41;42]. The overwhelming majority of treatments available for OA involve drugs and/or surgery. Despite strong evidence for the potent effect of mechanics (in particular, the external knee adduction moment) on disease progression and symptoms [38;43-47], there are few interventions that effectively reduce mechanical load. Our study results provide further evidence

that an intervention targeted to the reduction of mechanical load can have a durable therapeutic benefit with non-serious side effects that were largely managed with training or other minor adjustments.

There are a number of limitations of this study that warrant discussion. First, there was no control group without an intervention because of concerns about unblinding. Prior research has highlighted the difficulty of disentangling the placebo effect in non-pharmacologic clinical trials [40;48;49]. Consistent with this prior research, participants in the current crossover trial experienced symptomatic improvement during both the active and control intervention periods, making it more challenging to detect a relative improvement during the active intervention. There were also a number of dropouts in the trial. Most dropouts occurred during the second treatment condition, and efforts to reduce the impact of this censored data using an intent-to-treat analysis were applied [50]. Lastly, the daily duration of optimal treatment is unknown for this type of intervention, and therefore the prescribed 4 hours of daily use in this study was largely arbitrary. In the clinic, braces are often prescribed for use only during aggravating weight bearing activities.

There are also a number of important strengths of this study that merit discussion. The crossover design facilitates efficient recruitment and protection against confounding by patient-related factors. Similarly, we were adequately powered to detect a clinically meaningful treatment effect. The effect we found while statistically significant approximates that of clinical significance. Reports of the minimum clinically important difference in pain using the WOMAC suggest values reporting an improvement of 10-20% are of clinical importance [51;52]. It is possible that treatment effects may differ according to baseline alignment or radiographic severity. We are currently undertaking further research in this sample to determine if that is the case.

Multi-modal realignment therapy has significant effects on pain in persons with medial tibiofemoral OA. Further studies of this intervention are warranted to corroborate our findings. In addition, biomechanical studies that include clinical outcome measures will be helpful in determining whether clinical improvement is a function of mechanical alterations.

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Conflict of Interest Statement

The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication. The manuscript has not been submitted or is not simultaneously being submitted elsewhere, and no portion of the data has been or will be published in proceedings or transactions of meetings or symposium volumes.

There are no financial interests, direct or indirect, that might affect the conduct or reporting of the work submitted. The manuscript has been read and approved by all the authors, the requirements for authorship have been met, and each author believes that the manuscript represents honest work.

Author Contributions

DJH conceived and designed the study, supervised its conduct, drafted the manuscript and takes responsibility for the integrity of the work as a whole, from inception to finish. KDG and WH were also involved in the design of the study. All authors contributed to acquisition of the data and its interpretation. All authors critically revised the manuscript and gave final approval of the article for submission.

Table 1. Characteristics of the participants at baseline

Characteristics	Realignment to placebo (n=40)	Placebo to realignment (n= 40)
Age, mean _ SD years	63 (10.8)	60 (13.1)
Male sex, %	15 (37.5%)	15 (37.5%)
Body mass index, mean _ SD kg/m^2	32.7 (8.4)	34.7 (10.8)
Kellgren/Lawrence grade ≥3, %	39 (97.5%)	40 (100%)
Kellgren/Lawrence grade _2, %	1(2.5%)	0
Kellgren/Lawrence grade _3, %	25(62.5%)	28(70%)
Kellgren/Lawrence grade _4, %	14(35%)	12(30%)
Medial JSN Grade 0, %	1(2.5%)	0
Medial JSN Grade 1, %	9(22.5%)	10(25%)
Medial JSN Grade 2, %	14(35%)	16(40%)
Medial JSN Grade 3, %	16(40%)	14(35%)
Anatomic axis (degrees)	1.0(3.9) Median=1	0.7(5.3) Median=0
Contralateral knee Kellgren/ Lawrence grade≥2, %	32(80%)	30(75%)
WOMAC pain score, mean _ SD (0–20 scale)	9.2 (3.4)	9.1 (3.4)
WOMAC Function score, mean _ SD (0–68 scale)	33.3(11.8)	34.6(10.3)

* WOMAC _ Western Ontario and McMaster Universities Osteoarthritis Index.

Table 2. Predictors of WOMAC pain scores during the crossover trial*

Predictor	Model 1	Model2
Active Treatment (95% confidence interval) p-value	-1.78 -3.66, 0.11 0.06	-1.82 -3.05, -0.60 0.004
Treatment, period 1 vs. period 2 (95% confidence interval) p-value	-0.43 -2.38, 1.52 0.66	0.38 -1.61, 0.85 0.54
Carryover effect † (95% confidence interval) p-value	0.10 -2.94, 3.14 0.95	

* Values for model predictors are beta coefficients. For treatment as a predictor, a value of x means that active treatment was associated with a x lower score on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain scale compared with control treatment. An unstructured correlation matrix for observations within subjects was used in generalized estimating equation fitting of the marginal model (1). Model 2 was conducted with exclusion of the differential carryover effect.
† Tests whether treatment effects differed according to use in period 1 or period 2, constituting the differential carryover effect.

Table 3. Predictors of WOMAC function scores during the crossover trial*

Predictor	Model 1	Model2
Active treatment (95% confidence interval) p-value	-2.56 (-7.35, 2.24) 0.29	-2.90 (-6.60, 0.79) 0.12
Treatment, period 1 vs. period 2 (95% confidence interval) p-value	-0.58 (-5.23, 6.40) 0.84	-0.09 (-4.00, 3.82) 0.96
Carryover effect † (95% confidence interval) p-value	0.99 (-7.70, 9.68) 0.82	

* Values for model predictors are beta coefficients. For treatment as a predictor, a value of x means that active treatment was associated with a x lower score on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain scale compared with control treatment. An unstructured correlation matrix for observations within subjects was used in generalized estimating equation fitting of the marginal model (1). Model 2 was conducted with exclusion of the differential carryover effect.

† Tests whether treatment effects differed according to use in period 1 or period 2, constituting the differential carryover effect.

Table 4. Phase specific effects of each intervention§

	Treatment	Phase1		Phase2		Both Phases		Carryover effect test
		Mean change(SD)	Estimated Diff(SE)	Mean change(SD)	Estimated Diff(SE)	Mean change(SD)	Estimated Diff(SE)	
WOMAC Pain	Realignment	-2.2(3.3)	-1.9(1.01) p=0.068	-1.7(3.8)	-1.8(0.9) p=0.064	-2.0(3.5)	-1.8(0.6) p=0.004	0.10(1.5) p=0.947
	Placebo	-0.3(4.3)		0.03(3.2)		-0.1(3.7)		
WOMAC Function	Realignment	-5.1(12.1)	-3.5 (3.4) p=0.296	-4.6(9.6)	-2.6(2.4) p=0.290	-4.9(10.9)	-2.9(1.8) p=0.121	-0.99(4.3) p=0.82
	Placebo	-2.0(8.4)		-1.6(13.1)		-1.8(10.8)		

§ Incorporates the carryover effect test and the estimated treatment effect from model 2(without carryover effect)

Table 5. Adherence to and side effects of treatment

	Realignment	Placebo
Adherence, mean _ SD hours of wear/day		
Period 1	3.32(1.55)	3.99(2.82)
Period 2	3.35(2.39)	3.29(1.92)
Side effect, no. of patients		
Brace slipping/Positioning	16	4
Pain from shoes	7	1
Signal knee symptoms increasing	3	6
More pain in non-treatment knee	5	3
Other	7	5

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