Joint Mobilization of the Hands of Patients With Rheumatoid Arthritis: Results From an Assessor-Blinded, Randomized Crossover Trial

Adrian Levitsky, PhD,[a,b] Yogan Kisten, MTech,[a,b] Sara Lind, BSc,[c] Patric Nordström, BSc,[c] Helene Hultholm, BSc,[c] Jessica Lyander, BSc,[c] Viveka Hammelin, MSc,[a,d] Cidem Gentline, MD,[a,b] Ioanna Giannakou, MD,[a,b] Francesca Faustini, MD,[a,b] Eva Skillgate, PhD,[c,e] Ronald van Vollenhoven, MD, PhD,[a,f] and Tobias Sundberg, PhD[e,g]

Abstract

Objective: The purpose of this study was to assess the clinical feasibility and effectiveness of manual mobilization of the hands of patients with rheumatoid arthritis (RA).

Methods: A total of 320 individual hand joints were evaluated after recruiting an experimental research group of 12 participants with RA and, for clinical comparability, 8 participants with hand osteoarthritis (OA). One hand per participant was randomized to receive weekly low-grade (I-II) Kaltenborn manual mobilization, using passive sustained stretch of the metacarpophalangeal (MCP) joints II to V by licensed manual therapists. After 2 weeks, the randomized treated hand was crossed over to control (untreated) during weeks 3 to 4 and vice versa. Final assessment was at 2 months, which was 1 month after the last treatment at week 4. Primary hand outcomes included pain by visual analog scale, tender or swollen joint count, and presence of Doppler signal or synovial fluid and radiographic joint space by musculoskeletal ultrasound.

Results: In the RA group, both the initially randomized treated hand and the contralateral hand improved significantly from baseline to crossover to follow-up at 2 months (pain outcomes and Doppler signal, $P < .050$; synovial fluid and MCP joint space, $P \leq .001$). Hand pain and MCP joint space also improved significantly in OA. There were no dropouts or reported adverse events in either the RA or OA group.

Conclusion: In this study, manual mobilization of the hands of patients with RA was shown to be feasible, safe, and effective to integrate into specialized healthcare. (J Manipulative Physiol Ther 2019;42:34-46)

Key Indexing Terms: *Arthritis, Rheumatoid; Osteoarthritis; Musculoskeletal Manipulations; Integrative Medicine; Ultrasonography, Doppler*

Introduction

Rheumatoid arthritis (RA), the most common autoimmune inflammatory arthritis, affecting between 0.5% and 1% of adults globally, is a systemic disease that can lead to chronic pain, functional disability, bone damage, increased sick leave, and disability pension.[1-5] Despite major advances in treating this condition,[6-8] remission remains a difficult goal to achieve, and a substantial proportion of patients still experience chronic pain despite responding well to disease-modifying antirheumatic drugs (DMARDs),[9] stressing the need for proactive solutions in RA.

Manual joint mobilization is performed by various health professions, including licensed physiotherapists,

[a] Unit for Clinical Therapy Research, Inflammatory Diseases (ClinTRID), Department of Medicine, Solna, Karolinska Institutet and Karolinska University Hospital, Stockholm, Sweden.
[b] Rheumatology Unit, Department of Medicine, Solna, Karolinska Institutet and Karolinska University Hospital, Stockholm, Sweden.
[c] Naprapathögskolan – Scandinavian College of Naprapathic Manual Medicine, Stockholm, Sweden.
[d] Min Doktor International, Malmö, Sweden.
[e] Musculoskeletal & Sports Injury Epidemiology Center, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden.
[f] Amsterdam University Medical Centers (UMC), Amsterdam, The Netherlands.
[g] Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Stockholm, Sweden.
Corresponding author: Adrian Levitsky, PhD, Division of Innovative Care Research, Department of Learning, Informatics, Management and Ethics, Karolinska Institutet, Tomtebodavägen 18A, 171 77 Stockholm, Sweden.
(e-mail: *adrian.levitsky@ki.se, adrian.levitsky@gmail.com*).
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osteopaths, naprapaths, and chiropractors. Manual therapy techniques are typically implemented to normalize mobility and decrease pain in the management of musculoskeletal disorders, including osteoarthritis (OA). There is emerging evidence of the effectiveness for manual mobilization of extremity dysfunctions including shoulder and elbow pain, but there is limited literature regarding mobilization of the hands and wrists.[10]

Kaltenborn mobilization is a 3-tiered technique that incorporates small amplitude movements with traction to loosen and counteract any compressive forces on the joint (grade I), to gentle mobilization of joints with oscillations without overriding any tightening of the connective tissues surrounding the joint (grade II), or oscillations followed by additional stretching (grade III).[10-12] For hand joints, Kaltenborn mobilization thus far has been shown to reduce pain in the first carpometacarpal (CMC) joint and scaphoid bone in patients with CMC OA, to marginally improve pressure pain thresholds,[13,14] and to improve pressure pain thresholds and motor function in the contralateral (untreated) control hand compared to a placebo group that received a sham dose of intermittent ultrasound therapy.[15] To our knowledge, there are no published trials of Kaltenborn manual mobilization targeting its clinical feasibility and use in patients with RA.

To preliminarily assess the safety and effectiveness of Kaltenborn mobilization in patients with RA, we first conducted an initial 1-week small-scale single-arm pilot study in 5 women with RA who were all DMARD nonresponders with persistent color Doppler ultrasound activity, which previously has been reported in detail.[16,17] Here, repeated grade I to II mobilizations were chosen both for safety and feasibility and for investigating an immediate treatment dose–response relationship. The initial pilot study showed favorable results including reductions in pain, tenderness, and Doppler activity without reported adverse events.[16,17] The purpose of this current study was to assess the clinical feasibility and effectiveness of manual mobilization of the hands of patients with RA, and, for clinical comparability, in patients with hand OA.

Methods

This was a 2-month integrative, randomized blinded clinical feasibility trial to assess the clinical feasibility and effectiveness of Kaltenborn manual mobilization in a heterogeneous RA population. We included a target group of participants with hand OA—a diagnosis that is commonly treated with manual therapy and where previous benefits from manual mobilization have been reported.[13-15]

Research Participants, Recruitment, and Ethical Considerations

To be included in this clinical feasibility trial, research participants had to be 18 years or older and experience daily pain in the hands—with a diagnosis of RA or hand OA at least 6 months before inclusion. Criteria for exclusion were chronic bone damage or soft tissue injuries in the hands; acute inflammation within the latest week in any finger joints; any surgery on the shoulder, arm, or hand within the latest 3 months; or pregnancy within the latest 3 months.

All research participants were enrolled and then treated with Kaltenborn mobilization in the Rheumatology Clinic of the Karolinska University Hospital in Solna, Stockholm, Sweden. All participants were recruited either from the Rheumatology Clinic, the Karolinska University Hospital premises, or the Swedish Rheumatism Association (*Reumatikerförbundet*), and recruitment lasted from February 27, 2015, to December 14, 2016; concluding visit, February 8, 2017. The participants were instructed to continue their lifestyle as normal and to not make any changes to their background medication or to take new medications during the study period unless instructed by their physicians. To avoid treatment confounding, the participants were also asked to not take their medication the day of or the day before mobilization, particularly glucocorticoids or painkillers (if possible for them); to not attempt to learn or perform mobilization on themselves; and to not seek another care provider for mobilization treatment during the study. Written, informed consent was obtained from each research participant. This study was conducted in accordance to the Declaration of Helsinki and was approved by the regional ethical review board in Stockholm (EPN: *Regionalaetikprövningsnämndeni Stockholm*) with identification numbers 2013/2202-31 and 2014/2155-32.

Study Design and Randomization

The aim of this study was to assess the clinical feasibility, safety, and effectiveness of Kaltenborn manual mobilization of the hands in RA. This trial was registered on ANZCTR (ACTRN12617000696392, May 15, 2017). Research participants were randomized before the first data collection by computer-generated allocation stratified for RA/OA diagnosis to have one hand treated at baseline (BL) and week 2 (W2) whereby the contralateral hand served as the control (Fig 1); after 2 weeks there was a crossover and the initially treated hand became the control and vice versa, remaining throughout week 3 (W3) and week 4 (W4) to follow-up 1 month after the final treatment at W4 (Fig 2).

Health Care Providers, Blinding, Treatment, and Feasibility

Six joint-assessing physicians and the ultrasonographer were blinded to diagnosis, treatment, and the randomized hand. Five licensed Swedish manual therapists (4 naprapaths and 1 physiotherapist)—blinded to diagnosis, participant-reported outcome measures (PROMs), and physician/ultrasound evaluation—provided treatment, once per week, of the participants' metacarpophalangeal

(MCP) joints II to V with Kaltenborn within-the-slack grade I to II manual mobilization, which provides sufficient traction movements to counteract compressive forces in the joint while avoiding soft tissue stretching.[11,12] During each visit, it was inherently understood by the participants and therapists (including the physicians and ultrasonographer) that communication was not to be made regarding which hand was treated. At least 2 different manual therapists were assigned per participant and per hand, including 2 different physicians per participant. The therapist's treatment session would start with the participant sitting comfortably in front of a treatment table with their hand allotted for treatment facing palm up, relaxed, and being supported on a slight incline by a mobilization wedge or pillow, whichever was preferred. The manual therapist gripped the proximal and intermediate phalanges of the finger with one hand while the other hand gripped the metacarpus for stabilization. The therapist then applied Kaltenborn manual mobilization as described above to the MCP joint, and each respective MCP joint was treated for 3 minutes, followed by 1 minute of rest, and concluded with another 3 minutes before moving to the next MCP joint (7 minutes per joint, 28 minutes total).

The treatment sessions were scheduled directly after the data collection (PROMs and physician/ultrasound evaluations) at BL and W3, and directly before the data collection at W2 and W4 (Fig 2). Follow-up included only PROMs and physician/ultrasound evaluation. The study would be considered feasible upon completion if this schematic was followed without changes needed in the protocol, for example, the study could be successfully carried out in the hospital as intended without leading to problems such as slower patient flow or cumbersome staff workload.

Monitoring and Safety

The study coordinator obtained written, informed consent from each participant; randomized the participants in advance for hand treatment allocation, and ensured that the study followed the correct protocol at each visit, including allocation, following the appropriate time schedule and order of PROMs/assessments; and was also present to monitor the safety of the treatment. The participants were informed that they could end the treatment at any time should they wish to, and were asked while each treatment session was ongoing—both by the therapist as well as the coordinator—if the treatment was manageable for them.

Safety was a primary concern of this study, thus gentle low-velocity low-amplitude mobilization of nondestructed hand joints was performed. Safety in this study was assessed by the number of adverse events, and "safe" was defined as no serious adverse events or no adverse events leading to study dropout. In the case of any adverse event, an adverse event form would be filled which included a description of the event, intensity, and possible association to the treatment—and was available at all times during the study period. Monitoring for adverse events was active and physicians were on call for each study visit.

Assessments of Effectiveness: Outcomes and Data Collection

Pain Outcomes. At each visit, the following primary outcomes assessing pain were done: Pain was measured by 100-mm visual analog scale (VAS) before and after treatment and at follow-up. Hand pain was summed as a PROM hand-pain composite score: one for the MCPs II to V only (hand pain MCP); and one for the larger hand region, which included the MCPs II to V and the proximal and distal interphalangeal (PIP/DIP) joints II to III, respectively (hand pain region). The pain score for the hand region was chosen as it was a clinically relevant area both for RA (MCPs/PIPs) and OA (PIPs/DIPs). Among the participants with RA, a sample of 48 (randomized hand, H-rand) vs 48 (H-control) joints was assessed and analyzed for the MCPs and 96 vs 96 for regional pain, respectively (OA: 32 vs 32 and 64 vs 64, respectively) (n = 320 total).

Physician-reported outcomes included tender and swollen joint count of all joints of the hands, in addition to the wrists: 15 joints per hand or wrist.

Ultrasound Outcomes. Musculoskeletal ultrasound was performed using a GE Healthcare LOGIQ E9 ultrasound machine (Wauwatosa, Wisconsin) with previously described instrument presets[18-20] for the objective assessment of hand-joint inflammation. Primary outcomes (Table 1) included the automated quantification (Q) of joint activity using color Doppler pixel count calculations (% hyperemia/blood flow activity score within an inflamed joint: color Q-Doppler MCP/region), synovial fluid (area of hypertrophy and effusion, mm^2: synovial fluid MCP/region), and the radiographic distance (mm) between the MCP or interphalangeal bone space (joint space MCP/region).

Exploratory Outcomes. Additional exploratory (secondary) outcomes for each visit included pain by VAS of the MCP I joint and wrist, overall fatigue and global health by VAS (participant and physician-evaluated), the short form-36 survey for health-related quality of life, and the health assessment questionnaire. A modified clinical disease activity index (and a modified disease activity score measured at BL—where serology was available with acute-phase reactants C-reactive protein and erythrocyte sedimentation rate) was also measured based on counts of all hand joints (15 joints per hand or wrist), while excluding the knees, elbows, and shoulders. Exploratory ultrasound analyses included the previously described ultrasound measures applied to the MCP I joints (RA = 24, OA = 16) and the radial, midcarpal, and ulnar sections of the wrists (RA = 72, OA = 48).

Statistical Analyses

The independent samples Mann-Whitney U test, the paired samples Wilcoxon signed ranked test, or the Kruskal-Wallis test or Friedman test with Dunn-Bonferroni correction,

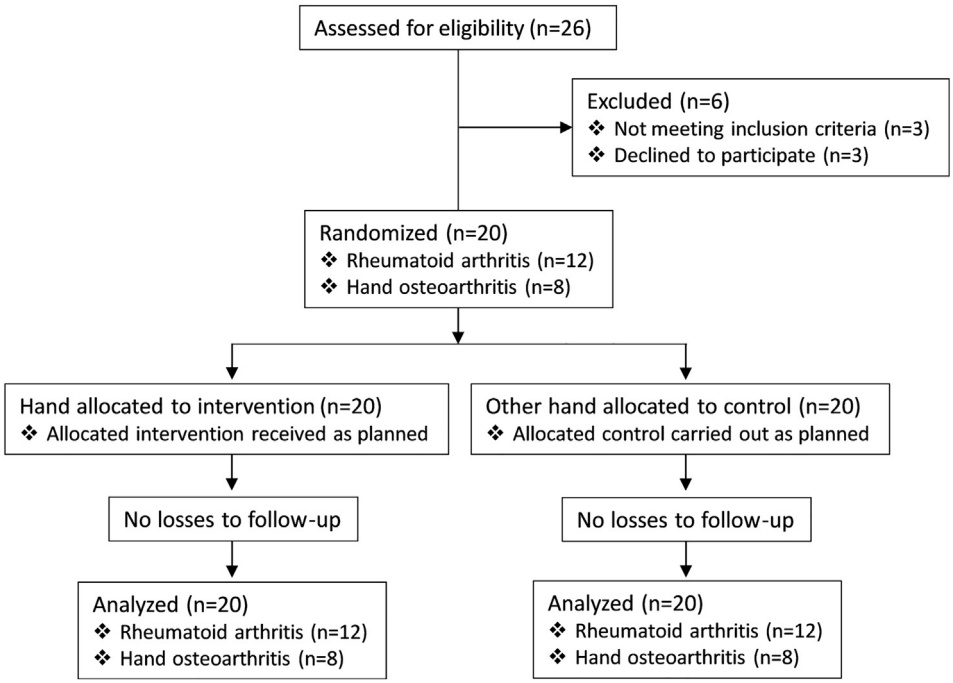

Fig 1. *Consolidated Standards of Reporting Trials flow diagram of participants included in the study.*

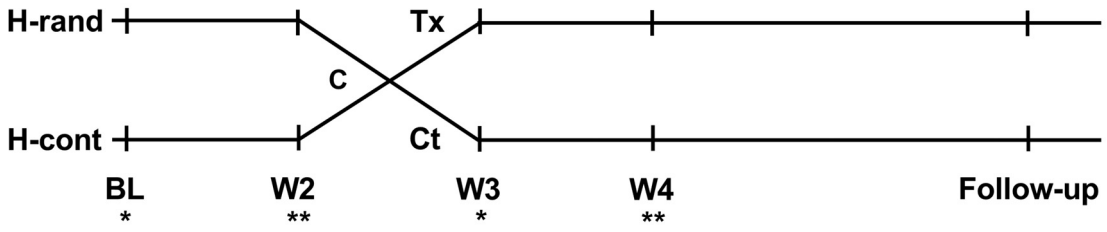

Fig 2. *Schematic of the randomized manual mobilization crossover trial. All research participants had a within-randomization: one hand was randomized for treatment (H-rand) for the first 2 weeks (treatment directly after BL and at W2), whereby the other would serve as a control (H-control) for this time period. Week 3 was the new BL whereby the former treated hand would now serve as a control and vice versa. Follow-up: 1 month after the final treatment at W4.*At BL and W3, most of the questionnaires as described under Methods were administered first (exception: post-treatment visual analog scales), followed by physician joint assessment and musculoskeletal ultrasound, and concluded with Kaltenborn mobilization treatment.**At W2 and W4, Kaltenborn mobilization treatment was performed first, followed by musculoskeletal ultrasound and most of the questionnaires as described under Methods (exception: pretreatment visual analog scales), and concluded with joint assessment by the physician.* BL, *baseline;* C, *crossover at W3;* Ct, *control hand (former treated);* H-cont, *control hand;* H-rand, *randomized hand;* Tx, *treated hand (former control);* W2, *week 2;* W3, *week 3;* W4, *week 4.*

respectively, were performed for continuous scale measures; Pearson χ^2 or Fisher exact test was performed with proportional categorical measures. All analyses were performed on IBM SPSS version 24.0 (IBM Corp, Armonk, New York). Two-tailed *P* values <.050 were considered significant.

Results

Research Participant Characteristics

A total of 320 individual hand joints were assessed in this study, and 12 research participants with RA (experimental group) and 8 participants with hand OA (clinical comparison group) were included and completed the study (n = 20, Fig 1). Parameters at BL did not differ across the groups, except that the participants with OA were significantly older and started with worse participant VAS global health (Table 1).The participants with RA were either on conventional synthetic DMARDs (primarily methotrexate) or were currently on biologics (primarily anti-tumor necrosis factor agents) (Supplementary Table S1). At the time of entry to the study, all participants with RA were considered to be on adequate antirheumatic therapy by their treating physicians, yet experienced mild to moderate pain in the hands. The participants with OA had moderate to high levels of hand

Table 1. *Baseline Parameters of Research Participants With RA or OA in the Randomized Kaltenborn Manual Mobilization Crossover Trial*

	RA (n = 12)		OA (n = 8)	
Proportions, n (%)				
Female sex	8 (67)		7 (88)	
Randomized hand (R)	7 (58)		3 (38)	
Dominant hand (R)	10 (83)		6 (75)	
Ever-smokers	7 (58)		5 (63)	
ACPA/RF positive	4/8 (50)		-	
Medians (IQR)				
Age	61 (49.5-63.8) [a]		69.5 (66.5-73) [a]	
Disease duration (y)	6 (1.1-6)		7 (4.3-19.3)	
Outcomes by hand	H-rand	H-control	H-rand	H-control
Hand pain MCP	1.5 (0-43.9)	7.3 (0-55.1)	10 (0-37.9)	15 (6.3-50.4)
Hand pain region	3.3 (0-49.1)	1.9 (0-40.8)	12.5 (0-46.9)	25 (6.3-50)
Swollen joints [b]	1.5 (0-3)	1 (0-3.8)	1.5 (1-2)	1 (0-2)
Tender joints [b]	4.5 (2.3-7)	4 (2.3-5)	4 (1.5-13)	5 (2.5-14.8)
Q-Doppler, MCP [c]	0 (0-2)	0 (0-22.2)	-	-
Q-Doppler, region [c]	0 (0-15.9)	0 (0-2.2)	-	-
Synovial fluid, MCP [c]	0 (0-7.2)	0 (0-2.5)	-	-
Synovial fluid, region [c]	0 (0-3.4)	0 (0-2.1)	-	-
Joint space, MCP	1.1 (1-1.3)	1.1 (1-1.3)	1 (0.9-1.1)	1 (0.9-1.1)
Joint space, region	0.9 (0.7-1.1)	0.9 (0.7-1.1)	0.8 (0.6-1)	0.8 (0.7-1)
VAS-pain (overall)	33.7 (15.1-71.3)		63.8 (42.3-85.9)	
Exploratory outcomes	H-rand	H-control	H-rand	H-control
Q-Doppler, wrist	0 (0-15.3) [c]	0 (0-4) [c]	-	-
Synovial fluid, wrist	0 (0-5.7) [c]	0 (0-7.4) [c]	-	-
M-CDAI [b]	19.6 (13.5-28)		22 (13.5-41.9)	
M-DAS28 [b]	4.7 (4-5.1)		-	
CRP/ESR	3 (1.3-4.8)/13 (9.5-24.8)		-	
HAQ	0.57 (0.25-0.94)		1.13 (0.13-1.47)	
SF-36 PCS	36.1 (31.7-40.7)		27.2 (20.1-40.1)	
SF-36 MCS	50.2 (43.5-56.9)		39.6 (30.1-54.6)	

Table 1. (*continued*)

	RA (n = 12)	OA (n = 8)
Fatigue, VAS	40.2 (16.9-69.6)	61.3 (24.6-91.3)
Global health, VAS	42.2 (17.3-60.3) [a]	64.5 (36-84.8) [a]
Global physician, VAS	22.4 (16.3-28.8)	31.7 (20-58)

ACPA/RF, anti-citrullinated protein antibody or rheumatoid factor positive; *CRP*, C-reactive protein; *ESR*, erythrocyte sedimentation rate; *ever-smokers*, current and past smokers; *HAQ*, health assessment questionnaire; *IQR*, interquartile range; *H-rand*, randomized hand; *H-control*, control hand; *Hand pain*, participant-reported pain intensity by VAS (0-100 mm) in the metacarpophalangeal, MCP joints II-V before treatment, followed by regional pain intensity among hand joints; *M-CDAI*, modified clinical disease activity index; *MCP*, metacarpophalangeal; *M-DAS28*, modified 28 joint-count disease activity score; *OA*, osteoarthritis; *Q-Doppler*, quantitative Doppler; *R*, right; *RA*, rheumatoid arthritis; *SF-36 MCS*, mental component score; *SF-36-PCS*, physical component score; *VAS*, visual analog scale.

Twelve participants with RA (minimum 6 months since diagnosis, range 0.7-27 years). Eight research participants with hand OA (minimum 6 months since diagnosis, range 1.5-36 years). Serostatus and acute-phase reactants were unavailable for these participants. Randomization: proportion of right, R vs left hand randomized; dominant hand: proportion R vs left. Region: MCP II-V + proximal and distal interphalangeal, joints II-III, respectively. Quantitative color Doppler musculoskeletal ultrasound activity indicates the absolute score (%) of hyperemia/blood flow activity within an inflamed joint; synovial fluid (area of synovial hypertrophy and fluid effusion by MSUS, mm^2); joint space (radiographic distance between the metacarpophalangeal or interphalangeal bone space, mm, measured by MSUS); VAS pain (overall); participant's fatigue and global health, respectively; followed by physician's global assessment of disease activity, measured by VAS.

Between-group differences (RA vs OA):

[a] Statistical significance ($P < .050$): age, $P = .002$; participant's VAS-global, $P = .047$.

[b] Swollen joints, tender joints, M-CDAI, and M-DAS28 were instead based on a modified physician's evaluation of the hands and wrists of the participants, including all DIPs/PIPs but excluding the shoulders, elbows, and knees.

[c] Owing to a limited number of participants expressing color Doppler signal or synovial hypertrophy or fluid effusion by MSUS, medians are shown with 5th to 95th percentiles in parentheses. The participants with hand OA had negligible signals or fluid.

pain. One participant with seropositive polyarticular juvenile idiopathic arthritis was included in the RA group owing to its similar disease manifestation. For comorbidities, see Supplementary material.

Pain Outcomes

Metacarpophalangeal Joints and the Hand Region. The participants with RA had significant reductions in MCP hand pain over 2 months ($P < .050$), regardless of which hand was being treated (Fig 3A). Both hands had significant reductions in pain from BL to W2/3, BL to W4, or BL to follow-up. Hence, the treatment order did not have any significant effect on the observed reductions of hand pain over time. However, a significant reduction was only seen from W3 to W4 when H-control was crossed over to treatment—a crossover for H-rand to control did not yield further significant reductions during this time frame (Fig 3A). Similarly, the pain of the hand region showed a comparable trend of improvement from BL to W2 or BL to follow-up, except that the change from BL to W3 was highly significant ($P \leq .001$), whereas W3 to W4 was not significant (Fig 3B).The greatest improvement in the joints individually was in MCP II, which started out with the highest pain (Supplementary Fig S1 and Table S2). Similar findings with highly significant reductions in MCP or regional hand pain were observed over 2 months among participants with OA ($P \leq .001$, Supplementary Fig S2).

Overall Pain. Pain by VAS in its entirety, which was assessed both before and after each treatment session, reduced significantly over 2 months among all participants with RA ($P < .050$, Supplementary Fig S3B). Significance was not maintained over 2 months in OA (Supplementary Fig S3C) unless combined with RA (Supplementary Fig S3A). Visual analog scale post-treated pain was generally lower after treatment than directly before treatment. All participants had self-reported tender joints before the physician's assessment. Here, participants reported improvements in their tender joints over 2 months; however, physician-based tender or swollen joint assessment did not improve over time (results not shown).

Ultrasound Findings

Quantitative Color Doppler Signal and Synovial Hypertrophy or Fluid Effusion. A total of 96 joints (8 per hand: MCPs II-V, PIPs/DIPs II-III) in 12 participants with RA were evaluated using color Doppler ultrasound quantification measures for active inflammation. Of these participants, 7 of 12 had no joint inflammation activity (0%) in the hands or wrists. The proportion of MCP joints that were synovitis positive (Doppler activity and synovial hypertrophy/effusion) decreased significantly from baseline to follow-up (randomized hand MCP joints: 20.8% [10/48] vs 8.3% [4/48]; initial control hand MCP joints: 18.8% [9/48] vs 10.4% [5/48]; $P \leq .025$, respectively). Significant decreases in Doppler quantification of regional joints were also observed at different points (control hand joints: BL-W2/3; randomized hand joints: BL-Follow-up, $P < .050$) (Fig 4). There was also a significant decrease of synovial fluid effusion volume (mm^2) from BL to follow-up in the MCPs ($P < .050$) and a highly significant reduction in the effused regional joints ($P \leq .001$) (Fig 4). The change from effusion presence to null from BL to follow-up for the hand region was also

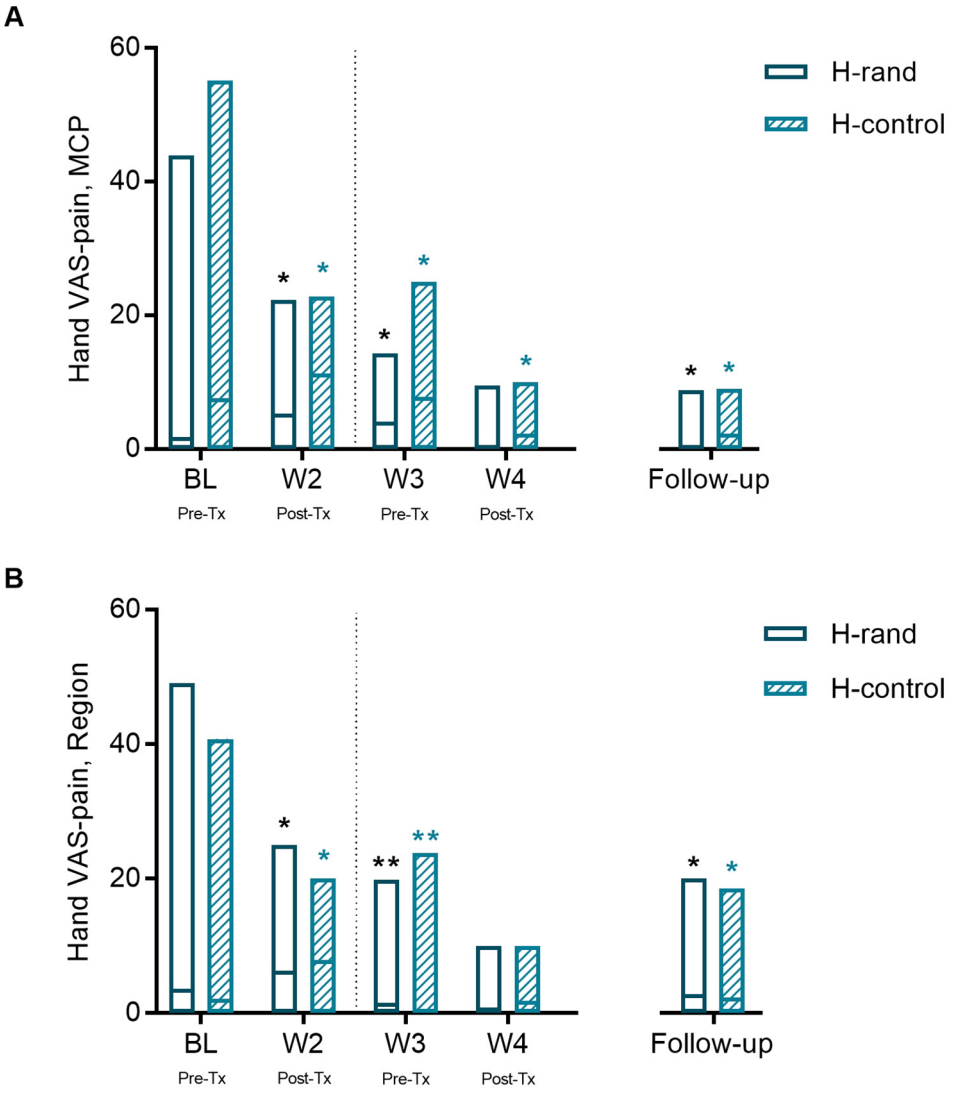

Fig 3. *Hand VAS for pain among participants with rheumatoid arthritis treated with Kaltenborn manual mobilization. (A) Hand-pain composite score by VAS, medians and interquartile ranges, among MCP joints II-V that were treated with Kaltenborn mobilization either from baseline to week 2 (BL-W2) (randomized hand, H-rand) or from W3-W4 (initial control hand, H-control) (n = 48 vs n = 48, respectively). (B) Regional hand-pain composite score among MCPs II-V in addition to the pain scores from the untreated proximal and distal interphalangeal (PIP/DIP) joints II-III (n = 96, H-rand vs n = 96, H-control, respectively). Dashed line indicates crossover at W3 (H-rand becomes control; H-control is now treated directly after the W3 assessment). Follow-up: 1 month after the last treatment at W4. Medians and interquartile range are plotted. H-rand vs H-control: no significant between-group differences. *Statistical significance of* P < .050 *or* **P ≤ .001. *BL vs W2: A. H-rand,* P = .046, *H-control,* P = .032; *B.* P = .002, *respectively. BL vs W3: A.H-rand,* P = .018, *H-control,* P = .009; *B.* P < .001, *respectively. Crossover: W3 vs W4: A. H-control (treated),* P = .018. *BL vs W4 (not plotted in figure): A. H-rand,* P = .007, *H-control,* P = .002; *B. H-rand/control,* P < .001, *respectively. BL vs follow-up: A. H-rand,* P = .029, *H-control,* P = .010, *B. H-rand,* P = .009, *H-control,* P = .025. BL, *baseline;* MCP, *metacarpophalangeal*; Post-Tx (W2 and W4), *VAS-pain directly after treatment with mobilization;* Pre-Tx, (BL and W3), *VAS-pain directly before treatment with mobilization;* VAS, *visual analog scale*; W2, *week 2;* W3, *week 3;* W4, *week 4.*

significant (randomized hand joints: 20.8% [20/96] vs 7.3% [7/96]; initial control hand joints: 18.8% [18/96] vs 8.3% [8/96]; $P \leq .004$, respectively). The participants in the hand OA arm had negligible Doppler activity or effusion.

Metacarpophalangeal Joint Space

The MCP radiographic joint space of the participants with RA, which was measured between the central tip of the phalanges to the central tip of the metacarpal bone by musculoskeletal ultrasound, increased significantly from BL to W2 or W3 to W4, regardless of which hand was treated ($P < .050$, Fig 5). From BL to W3, BL to W4, or BL to follow-up, highly significant increases were observed ($P \leq .001$); namely, joint space from BL to follow-up increased from 1.1 to 1.4 mm (median 21.2% increase [interquartile range 10.3%-32.8%]). Improvements in MCP joint space, synovial fluid (A-B), and Doppler activity (C-D) over 2 months

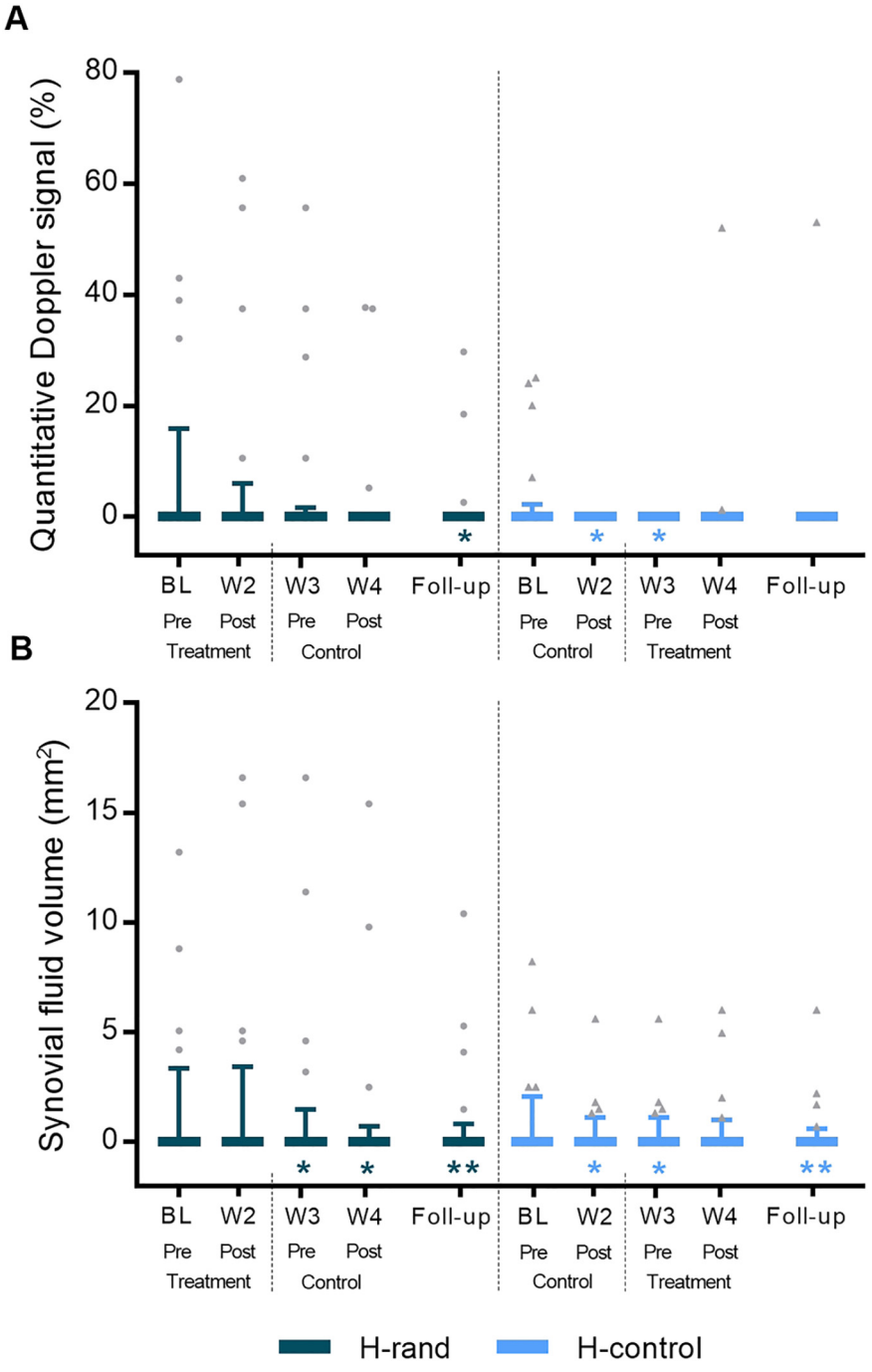

Fig 4. *Ultrasound analysis of the hand region with quantitative color Doppler signal and synovial fluid volume among participants with rheumatoid arthritis treated with Kaltenborn manual mobilization. (A) Quantitative color Doppler musculoskeletal ultrasound signal composite score among the hand region (metacarpophalangeal joints II-V + proximal and distal interphalangeal joints II-III), with MCP II-V treated with Kaltenborn mobilization either from baseline to week 2 (BL-W2) (H-rand) or from W3-W4 (H-control) (n = 96 vs n = 96). (B) Synovial hypertrophy or fluid volume composite score for the hand region. Dashed line indicates crossover at W3 (H-rand becomes control; H-control is now treated directly after the W3 assessment). Follow-up: 1 month after the last treatment at W4. Pre (BL and W3): score directly before treatment with mobilization; Post (W2 and W4): score directly after treatment with mobilization. Most participants had no Doppler activity or synovial hypertrophy or fluid effusion (medians, interquartile range = 0, respectively), thus medians with 95th percentiles (bars) are plotted and outliers are indicated above the 95th percentiles in gray. BL vs W2/W3: A. H-control,* P = *.043, respectively; B. H-control,* P = *.014, respectively. BL vs W3: B. H-rand,* P = *.016. Crossover: W3 vs W4: B. H-rand (untreated),* P = *.007. BL vs W4 (not plotted in figure): B. H-rand,* P = *.013, H-control,* P < *.001. BL vs Follow-up: A. H-rand,* P = *.028; B. H-rand,* P = *.001, H-control,* P < *.001. Between-group differences, H-rand vs H-control, A. W2,* P = *.024; W3,* P = *.044. *Statistical significance of* P < *.050 or* **P ≤ *.001.* BL, *baseline;* Foll-up, *follow up;* H-control, *initial control hand;* H-rand, *randomized hand;* W2, *week 2;* W3, *week 3;* W4, *week.*

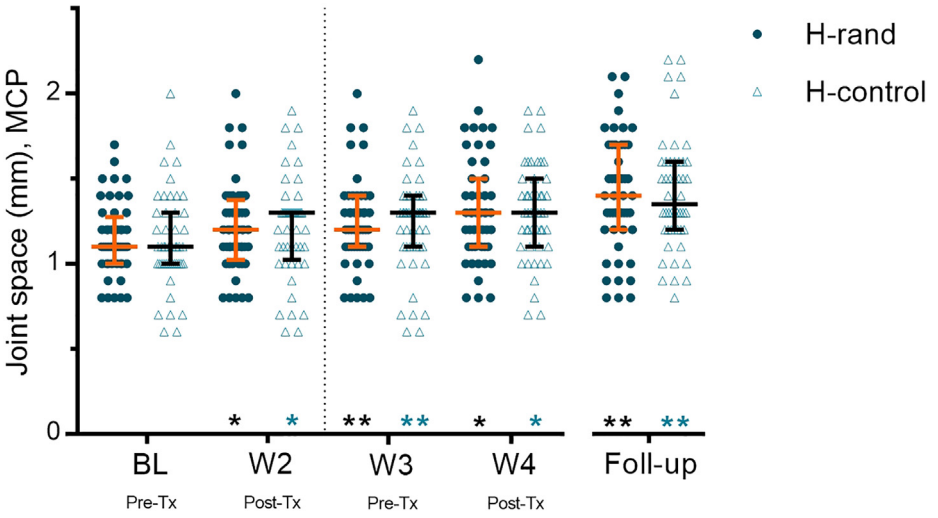

Fig 5. *Metacarpophalangeal joint space among participants with rheumatoid arthritis treated with Kaltenborn manual mobilization. Metacarpophalangeal joint space (between tip of phalanges to tip of metacarpus) among MCP joints II-V that were treated with Kaltenborn mobilization either from BL-W2 (H-rand) or from W3 to W4 (H-control) (n = 48 vs n = 48, respectively). Follow-up: 1 month after the last treatment at W4; Pre-Tx (BL and W3), joint space directly before treatment with mobilization; Post-Tx (W2 and W4), joint space directly after treatment with mobilization. Medians and interquartile ranges are plotted in addition to each individual value. H-rand vs H-control: no significant between-group differences. Statistical significance of* *P < .050 or* **P ≤ *.001. BL vs W2: H-rand,* P = *.018, H-control,* P = *.003; BL vs W3: H-rand,* P = *.001, H-control,* P < *.001. Crossover: W3 vs W4: H-rand (untreated),* P = *.002, H-control (treated),* P < *.001. BL vs W4 (not plotted in figure): H-rand/control,* P < *.001, respectively. BL vs follow-up: H-rand/control,* P < *.001, respectively.* BL*, baseline;* H-control*, initial control hand;* H-rand*, randomized hand;* MCP*, metacarpophalangeal;* Post-Tx*, post treatment;* Pre-Tx*, pre treatment;* W2*, week 2;* W3*, week 3;* W4*, week 4.*

are shown in Figure 6. The participants with OA started out with less MCP joint space, and a large increase was observed from BL to follow-up, from 1.0 to 1.4 mm (26.7% [23.1-35.2%]) (Supplementary Fig S4). The same pattern was seen in the total regional joint space, but joint space of DIPs/PIPs specifically did not increase (results not shown).

Exploratory Outcomes

Among all participants combined, highly significant reductions in overall fatigue were noted immediately after treatment post-BL, and from BL to W3 or BL to W4 ($P \leq .001$, Supplementary Fig S5A). Sustained significant reductions in fatigue were observed in most comparisons versus BL among those with RA ($P < .050$, Supplementary Fig S5B), and up to W4 for participants with OA (Supplementary Fig S5C). For additional exploratory outcomes, moderate improvements by ultrasound in the wrists were observed—in addition to pain in the MCP I joint—for the randomized hand among participants with RA; and nonsignificant improvements were seen in other outcome measures (see Supplementary material for more details).

Discussion

We examined in an assessor-blinded, intra-subject randomized crossover trial whether Kaltenborn manual mobilization of the hands could be applied safely to participants with RA and how it affected symptoms and ultrasound measures in the treated joints. This study is, to our knowledge, the first examination of its kind in RA. It was feasible to apply the Kaltenborn manual mobilization technique in the clinical setting, and the results indicate that this is a relatively safe integrative treatment option with potential and similar benefits for participants with RA and OA alike. Nevertheless, significant subjective and objective improvements were seen in both hands before and after the crossover point, and although we are unable to rule out a potential placebo effect or regression to the mean, we remain open to the possibility that the observed improvements might be related to the manual therapy treatment. The changes demonstrated by ultrasound for radiographic joint space and synovial fluid lend support to this possibility and suggest that the mobilization might induce a restorative effect in both hands. Further studies are needed to confirm this.

Comparisons to Previous Findings

We previously showed, in our initial pilot study, significant reductions in pain, tender joints, and quantitative Doppler signal in 5 women with active RA who were nonresponsive to DMARDs.[16,17] Here, ultrasound was not performed on the control hand, but we did see that the control hand also had significant reductions in pain, which

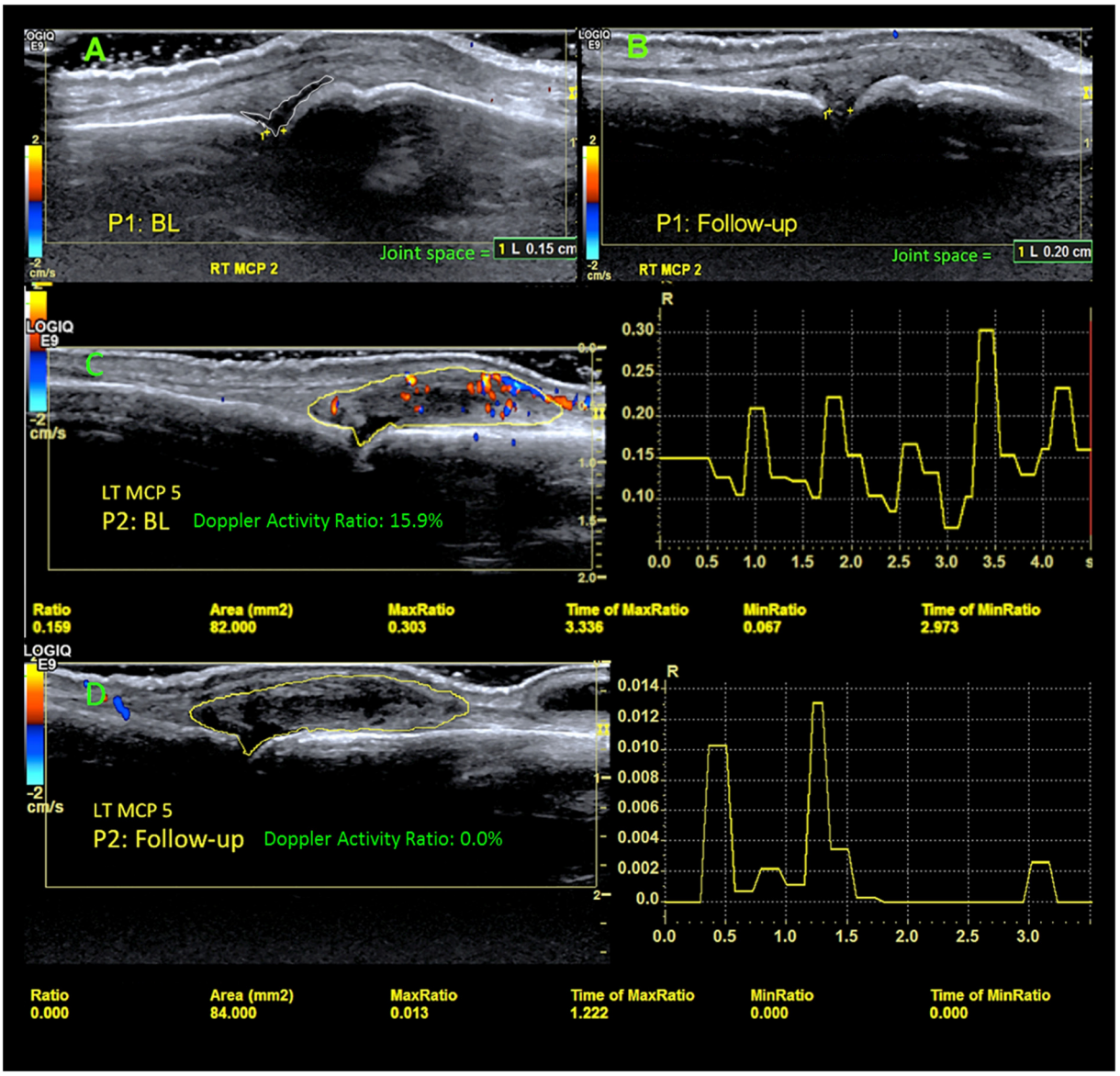

Fig 6. *Changes in MCP joint space, synovial fluid, and Doppler activity in rheumatoid arthritis over 2 months with Kaltenborn manual mobilization. The following images are from 2 participants (P1, A-B; and P2, C-D, respectively) with rheumatoid arthritis included in this study who gave consent to publication of their musculoskeletal ultrasound images. (A-B) Metacarpophalangeal joint space of P1 at baseline (BL, 1.5 mm) and follow-up 1 month after the final treatment at W4 (2.0 mm), respectively, including presence of synovial fluid at BL (0.8 mm^2), which is gone by follow-up. (C-D) Presence of active Doppler quantification of P2 at BL (ratio, 15.9%; max: 30.3%), which is virtually gone by follow-up (ratio: 0%; max: 1.3%), respectively.* BL*, baseline;* LT*, left;* MCP*, metacarpophalangeal;* P*, participant;* RT*, right;* W4*, week 4.*

we confirm and expand on in our current randomized controlled crossover pilot study. The current treatment protocol with Kaltenborn manual mobilization was the same as in the initial pilot study, except that there the treated hand received 2 back-to-back treatment sessions (56 minutes total) on 3 occasions within a week, and 3 ultrasounds were carried out on the treated hand at BL and after 1 week: before treatment, after the first treatment session (first 28 minutes), and after the second treatment session (final 28 minutes). Most participants in the previous study had an active MCP II to V Doppler signal (mean 52% activity), and we observed a marked reduction (mean 21%) in quantitative Doppler signal from BL pretreatment versus the final treatment session after 1 week.[16,17] In our current study, most MCPs had no signal (mean 1.1%, median 0%, maximum 32.1% activity). Nonetheless, despite the limited overall inflammation, the total counts of active versus inactive MCP II to V joints expressing synovitis decreased by 8.4% to 12.5%, depending on the hand, over 2 months. Because improvements were observed both in the control and treated hands, we are unable to rule out a potential placebo effect or regression to the mean. As indicated earlier, however, manual mobilization has

previously led to treated and contralateral improvements in CMC OA.[13-15] This, together with the noteworthy pain reductions and objective improvements we currently observed in joint space, synovial fluid, and quantitative Doppler signal, indicates that the method may induce restorative effects on the body. In the treated hand, traction (mobilization) has thus far been documented to create a vacuum phenomenon followed by joint space widening as measured by X-ray of the MCP II in 22 healthy participants.[21] This phenomenon could hypothetically assist the joint in clearing out or eliminating excessive synovial fluid. In addition, mobilization may work on inflammation similarly as massage therapy— which has been shown to reduce cytokines anti-tumor necrosis factor and interleukin 6 while promoting mitochondrial biogenesis.[22]

Limitations and Future Research

The primary limitation of this study is that it was a monocentric study with a rather small sample size. However, a large proportion of joints were assessed with PROMs and by blinded physician and ultrasound evaluation. Despite a limited proportion of joints expressing Doppler activity and synovial hypertrophy or fluid effusion in this study, positive effects were observed throughout the study duration of 2 months. Future studies interested in using crossover designs should consider the length of time it may take for pain to come back to the BL point if it occurs. The limitation of our crossover design was that W3 might have been a switch that occurred too soon, as W3 started off with significantly lower pain and other outcome measures as a result of mobilization—thus it was more difficult to see improvements or differences afterward. Perhaps a more long-term treatment protocol before crossover is required to note any differences in the treated versus untreated hand (as we observed no differences in improvement from BL to W2/W3), in addition to a longer period of no treatment before the crossover to observe a potential washout effect emulating the BL measure. Having a within-subject control design also appears to be a limitation of comparing the potential superiority of treating one side vs the untreated contralateral side. Although massage therapy has, for example, been shown to inhibit pro-inflammatory markers while promoting tissue repair compared to the control leg after exercise-induced muscle injury,[22] several studies have demonstrated that treating one side of the body systemically improves the other, such as strength or range of motion with various exercise modalities,[23-28] in addition to contralateral pain analgesia by transcutaneous electrical nerve stimulation.[29-31] Thus, a standard-of-care control RA group ought to be included as a future step. We cannot definitively explain how the untreated hand from BL to W2/W3 had similar objective joint improvements as the treated hand. Participants were specifically instructed not to emulate the treatment on their hands or to seek out other manual therapists during the study, although there were no means to verify compliance. At this point, we can only hypothesize as a basis of our results that mobilization on one hand may have a systemic effect on the other.

The strengths of the study are that we have been able to quantify a subjective feeling of pain and fatigue relief with objective improvements in the joints, and we have been able to control for several biases with the following setup: at least 2 different manual therapists (blinded to diagnosis, outcomes, and physician/ultrasound evaluation) per participant and per hand; 2 different physicians (blinded to diagnosis, treatment, outcomes, and ultrasound) per participant; and the ultrasonographer (blinded in the same manner as physicians), for image analysis, randomly selected a participant's ultrasound images to be analyzed with the study coordinator (blinded to the selection and thus the treated hand), and both used the ultrasonographic reference atlas by Hammer et al[32] and resolved any disputes by consensus. To prevent overestimation of joint space for all visits beyond BL, the ultrasonographer recorded the joint space conservatively with slight under measurement. In addition, the first selected participant's ultrasound images were measured as a pilot and then independently remeasured a second time. The measurements yielded no to minimal discrepancy (<5%) across all images. Finally, we have been able to design a relatively successful and clinically feasible treatment session that could, with more studies, be potentially incorporated into clinics and hospitals as a form of integrative health care. The study feasibility is reflected by the fact that we had no dropouts and an average follow-up time of 1 month was followed. With this in mind, a limited amount of sessions (once per week, 28 minutes each) within 4 weeks may contribute to valuable clinical improvements in RA that are sustainable without a washout effect after 1 month.

Future research is needed to verify the emerging positive results concerning pain and objective improvements by means of larger randomized controlled trials. The apparent synergistic effect on the contralateral hand also needs to be evaluated physiologically. Interviews or focus group discussions could be used to address the perceived effects of manual mobilization from the patients' perspectives and to help postulate hypotheses about where the therapeutic effect comes from, for example, from the procedure itself or from the totality of the treatment session including interaction with the therapist. Finally, to assess the potential causal effects of manual mobilization on reducing Doppler quantification and synovial hypertrophy or fluid as markers of inflammation, a larger proportion of participants with inflamed joints should also be studied further.

Conclusion

To our knowledge, this is the first study to investigate Kaltenborn manual mobilization of the hands as a potential integrative treatment option in RA. The results suggest that this type of low-grade manual therapy treatment appears feasible, safe, and effective to integrate in the clinical setting with subjective and objective improvements being

observed over 2 months both in participants with RA and OA. Although the similar improvements in either hand could suggest a placebo effect or regression to the mean, it cannot be ruled out that joint mobilization may have a bilateral systemic effect via the central nervous system that may affect both hands.

Appendix A. Supplementary Data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmpt.2018.04.007.

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Contributorship Information

Concept development (provided idea for the research): A.L.
Design (planned the methods to generate the results): A.L., R.vV., T.S.
Supervision (provided oversight, responsible for organization and implementation, writing of the manuscript): R.vV., T.S.
Data collection/processing (responsible for experiments, patient management, organization, or reporting data): A.L.
Analysis/interpretation (responsible for statistical analysis, evaluation, and presentation of the results): A.L., Y.K.
Literature search (performed the literature search): A.L., T.S.
Writing (responsible for writing a substantive part of the manuscript): A.L.
Critical review (revised manuscript for intellectual content, this does not relate to spelling and grammar checking): A.L., Y.K., S.L., P.N., H.H., J.L., V.H., C.G., I.G., F.F., E.S., R.vV., T.S.
Other (list other specific novel contributions): All authors meet the International Committee of Medical Journal Editors guidelines for authorship and contributed to the discussion of the results and to the preparation of the manuscript. Y.K. conducted ultrasound for all visits and, together with A.L., prepared and quantified the ultrasound images. S.L., P.N., H.H., J.L., and V.H. performed Kaltenborn manual mobilization on the participants. C.G., I.G., and F.F. performed joint evaluations of the hands and wrists. E.S. is a senior author and manual therapy subject-matter expert. All authors read and approved the final version of the manuscript.

Practical Applications

- This was the first randomized trial demonstrating the safety and effectiveness of Kaltenborn manual mobilization in treating patients with RA.
- Alleviation of pain, reduction in swelling and inflammation of the joints, and MCP joint space widening were the key findings of this study.
- Our methodology and findings inform future investigators what to consider if large randomized controlled trials and other studies involving mobilization are to be performed in RA and warrants further investigation of how mobilization may stimulate the central nervous system to produce the systemic subjective and objective improvements in our study.

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