Effectiveness of an Ayurveda treatment approach in knee osteoarthritis - a randomized controlled trial

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Abstract: OBJECTIVE Ayurveda is commonly used in South Asia to treat knee osteoarthritis (OA). We aimed to evaluate the effectiveness of Ayurvedic treatment compared to conventional conservative care in patients with knee OA. METHOD According to American College of Rheumatology (ACR) criteria knee OA patients were included in a multicenter randomized, controlled, open-label trial and treated in 2 hospital clinics and 2 private outpatient clinics in Germany. Participants received either a multimodal Ayurvedic treatment or multi-modal conventional care with 15 treatments over 12 weeks respectively. Primary outcome was the change on the Western Ontario and McMaster University Osteoarthritis (WOMAC) Index after 12 weeks. Secondary outcomes included WOMAC subscales; the pain disability index and a pain experience scale, numeric rating scales for pain and sleep quality, quality-of-life and mood, rescue medication use, and safety issues. RESULTS One hundred fifty-one participants (Ayurveda n = 77, conventional care n = 74) were included. Changes of the WOMAC Index from baseline to 12 weeks were more pronounced in the Ayurveda group (mean difference 61.0 [95%CI: 52.4;69.6]) than in the conventional group (32.0 [95%CI: 21.4;42.6]) resulting in a significant between-group difference ($p < 0.001$) and a clinically relevant effect size (Cohen's d 0.68 [95% CI:0.35;1.01]). Similar trends were observed for all secondary outcomes at week 12. Effects were sustained at follow-ups after 6 and 12 months. CONCLUSION Results suggest that Ayurvedic treatment is beneficial in reducing knee OA symptoms. Further studies should be conducted to confirm the magnitude of the effect and to clarify the role of different treatment components and non-specific effects. REGISTRATION: at clinicaltrials.gov (NCT01225133; initial release 10/06/2010).

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Effectiveness of an Ayurveda treatment approach in knee osteoarthritis – a randomized controlled trial

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SUMMARY

Objective: Ayurveda is commonly used in South Asia to treat knee osteoarthritis (OA). We aimed to evaluate the effectiveness of Ayurvedic treatment compared to conventional conservative care in patients with knee OA.

Method: According to American College of Rheumatology (ACR) criteria knee OA patients were included in a multicenter randomized, controlled, open-label trial and treated in 2 hospital clinics and 2 private outpatient clinics in Germany. Participants received either a multi-modal Ayurvedic treatment or multi-modal conventional care with 15 treatments over 12 weeks respectively. Primary outcome was the change on the Western Ontario and McMaster University Osteoarthritis (WOMAC) Index after 12 weeks. Secondary outcomes included WOMAC subscales; the pain disability index and a pain experience scale, numeric rating scales for pain and sleep quality, quality-of-life and mood, rescue medication use, and safety issues.

Results: One hundred fifty-one participants (Ayurveda n = 77, conventional care n = 74) were included. Changes of the WOMAC Index from baseline to 12 weeks were more pronounced in the Ayurveda group (mean difference 61.0 [95%CI: 52.4;69.6]) than in the conventional group (32.0 [95%CI: 21.4;42.6]) resulting in a significant between-group difference ($p < 0.001$) and a clinically relevant effect size (Cohen's d 0.68 [95% CI:0.35;1.01]). Similar trends were observed for all secondary outcomes at week 12. Effects were sustained at follow-ups after 6 and 12 months.

Conclusion: Results suggest that Ayurvedic treatment is beneficial in reducing knee OA symptoms. Further studies should be conducted to confirm the magnitude of the effect and to clarify the role of different treatment components and non-specific effects.

Registration: at clinicaltrials.gov (NCT01225133; initial release 10/06/2010).

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Introduction

Osteoarthritis (OA) is of global relevance with up to 250 million people being affected from knee OA worldwide[1–4]. Despite progress in conventional knee OA management many patients continue to be affected from pain and disability and there is a need for further effective treatment approaches[5–7]. In India and South Asia traditional Ayurvedic medicine is also commonly used as a treatment approach in knee OA and the World Health Organization (WHO) recommends to include traditional systems of medicine in global health care[8,9].

In India Ayurveda is recognized and regulated by an independent ministry (AYUSH)[9–11]. Ayurveda uses individualized treatments consisting of multi-modal components such as manual therapies, nutritional therapy and herbs, lifestyle counseling and yoga-based exercise[12] (Appendix 1).

A review of 33 Ayurveda studies showed that most trials (91%) evaluated herbal preparations as single interventions[13]. No clinical trial evaluated Ayurveda treatment with its multi-modal components for knee OA so far[14].

In western countries, knee OA is treated by conventional multimodal interventions combining pharmacological and non-pharmacological interventions[7,15,16]. Ayurveda also uses a multimodal intervention approach for the treatment of knee OA. Comparisons of the effectiveness of conventional and Ayurveda interventions for the treatment of knee OA would be a feasible research question.

Method

Study design

Protocol details have been published previously. We designed a multicenter open-label trial and randomized participants to 12 weeks of Ayurveda or conventional guideline-based care (Appendix 2)[14,17]. Outcomes were assessed at baseline, 6 weeks, 12 weeks, 6 months and 1 year. Participants received 15 treatment sessions within 12 weeks. Long-term effects were evaluated after 6 and 12 months (Fig. 1).

We used an equal block-randomization with variable block size and stratified for study site. An independent statistician generated a randomization list with SAS (version 9.1, SAS Inc, Cary, NC). The data manager transferred the randomization list into a secure database (Microsoft Office Access 2007), where the randomization list was not accessible to anyone else. Each participant could be registered and randomized only once and the database did not allow deleting participants' data. Statisticians, data entry personnel and the funding source were blinded to treatment assignment throughout the study.

The trial was registered at clinicaltrials.gov under NCT01225133 and was approved by the university ethics committee (Charité Medical University, EA1/124/10). It followed the Declaration of Helsinki and Good Clinical Practice guidelines for trial conduct. Participants provided written informed consent before taking part and were not reimbursed for participation. Due to changes in ethical regulations during the trial one amendment has been made regarding the provision of nutritional supplements. Thereafter, the remaining 24 study participants from the Ayurveda group did not receive nutritional supplements but were advised to increase the food intake of the previously supplemented nutrients as much as feasible.

Participants

Seventy percent of participants were recruited via newspaper advertisements. The remaining participants were recruited by physicians from the trial center clinics or contacted the centers themselves, because they had heard about the trial. Participants were pre-screened over the phone and if suitable scheduled to an enrolment visit (Fig. 2).

Inclusion criteria: male or female, 40–70 years of age; knee OA pre-diagnosed by an orthopedic surgeon or radiologist according to American College of Rheumatology (ACR) criteria[18,19]; radiologic changes in X-ray (Kellgren–Lawrence $\geq$ 2[20,21] or an MRI Recht grading score $\geq$ 2(a)[22,23]; mean baseline pain intensity in the affected knee of $\geq$40 mm on a 100 mm visual analogue scale (VAS) over 7 days preceding enrollment, written informed consent.

Exclusion criteria: knee pain caused by congenital dysplasia, rheumatoid arthritis, autoimmune diseases, malignancies, knee surgery or knee-arthroscopy; administration of chondroprotective drugs, intra-articular injections into the knee joint or systemic corticosteroid medication during the 3 months preceding enrollment; start of any new treatment for knee OA during the 4 weeks preceding enrollment including treatment with paracetamol, OTC NSAIDs and any CAM treatments; pregnancy or breastfeeding; acute mental disorders; serious acute organic diseases; serious chronic co-morbidity; obesity $\geq$ WHO grade II; blood coagulation disorders; intake of coagulation-inhibiting medication other than acetylsalicylic acid and clopidogrel; invasive measures at the affected joint during the 12 weeks preceding enrollment or planned for the 12 months following enrollment; and being in the process of applying for pension/disability benefits.

Interventions

The interventions were developed in an international consensus process with Ayurveda and orthopedic experts from three countries (India, Germany and Italy) using a Delphi approach[24]. Ayurvedic literature (Ayurveda group)[12,25], and current guidelines (conventional group) were used[16,26,27]. Ayurveda was provided by conventionally trained physicians with additional Ayurveda training, who had undergone either a university program for Ayurveda in India (Bachelor of Ayurveda Medicine and Surgery [B.A.M.S.] Indian expert) or had $\geq$ 500 hours of academic training in Ayurveda plus $\geq$ 2 years of continuous clinical experience with Ayurveda (European experts). Other involved Ayurvedic therapists were required to have $\geq$2 years of continuous clinical experience in their fields (manual therapies, nutritional advice, lifestyle advice, yoga therapy). To assure treatment quality, line of treatment for the first 30 participants was discussed by 4 Ayurveda doctors until consent was achieved. In the conventional group interventions were prescribed by board certified medical doctors (MDs) specialized in orthopedics or orthopedic surgery. All other conventional therapists (physiotherapy, occupational therapy) required a completed licensed training in their field and a minimum of $\geq$2 years of continuous clinical experience. In total 5 specialized physicians (2 Ayurveda, 3 conventional MDs) and 20 specialized therapists (12 Ayurveda [8 for manual therapies, 2 for yoga, 2 for nutrition and lifestyle], 8 conventional [6 for physiotherapy, 2 for nutrition and occupational therapy]) treated participants in 2 public hospital outpatient clinics and 2 hospital affiliated private outpatient clinics for Ayurveda, orthopedics, orthopedic surgery, physiotherapy and occupational therapy in Berlin, Germany. Treatments in both groups were administered in 15 sessions over 12 weeks (2 sessions/week in the first 3 weeks and 1 session/week in weeks 4–12), with treatment time between 45 and 50 min (conventional) and 60–90 min (Ayurveda) per session. Treatment time between groups was not further equalized as a treatment time >50 min per session for physiotherapy/exercise would have largely exceeded existing treatment standards for knee OA patients.

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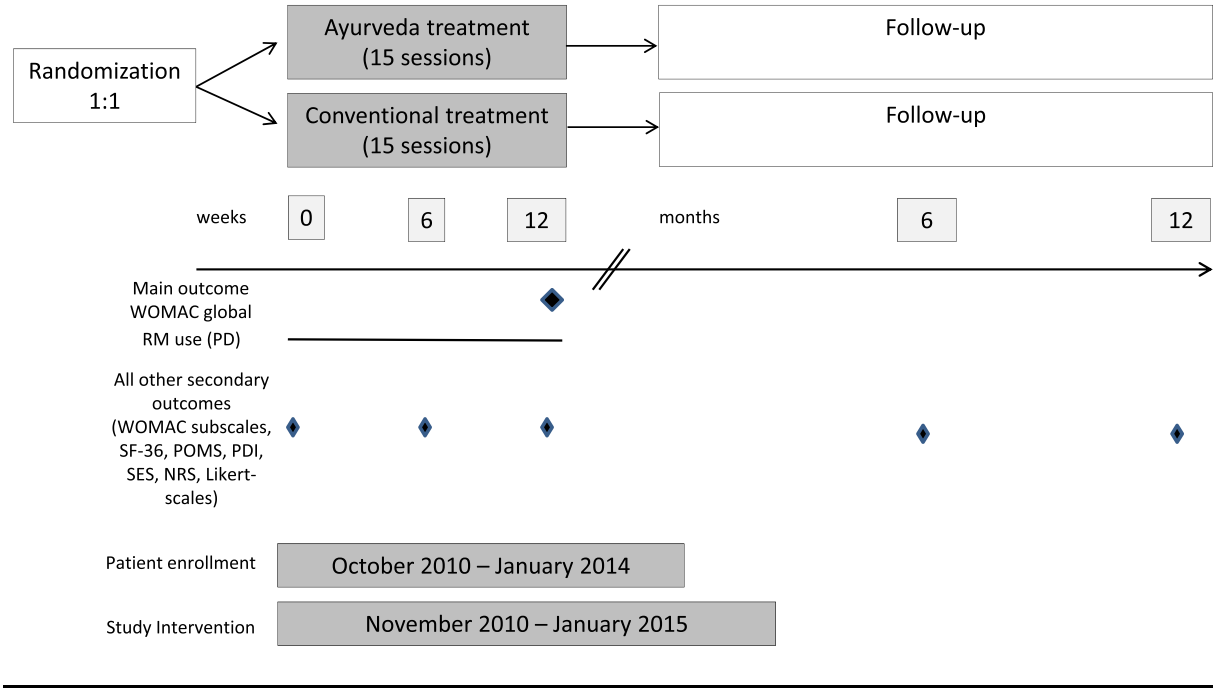

Fig. 1. Study design.

The multi-modal Ayurveda intervention was individualized and followed the treatment principles of Ayurveda. Individualized treatment included specific manual treatments and massages; Ayurvedic diet counseling including specific consideration of selected food items, adapted to local food items commonly available in German grocery stores; two nutritional Ayurvedic supplements typically used for painful conditions of the musculoskeletal system, Ashvagandha (Withania somnifera Dunal. Linn) and Yogaraja Guggulu (compound supplement, main ingredient Commiphora mukul Hook. ex Stocks); general and specific Ayurvedic lifestyle advice; knee specific yoga posture advice; and daily self-applied knee massage.

Conventional group participants received multi-modal and individualized conventional care for knee OA according to current guidelines; this included quadriceps muscle strengthening exercises, knee specific physiotherapy including manual therapy, occupational therapy, advice for individual home knee exercises, dietary advice for weight loss for overweight participants, and, if necessary, administration of long-term pain medication according to current guidelines[16,26,27] (Appendix 2f).

In both groups rescue medication with a maximum of 3 g paracetamol per day could be used. In case of intolerance or non-response to paracetamol, topical or oral NSAIDs could be used (e.g., diclofenac-sodium ointment 3 time per day or oral ibuprofen up to a maximum dose of 800 mg per day or equivalent) after having consulted a study physician. The use of other pain medication was discouraged. Participants were instructed to document the use of pain medication in diaries during the intervention period.

Outcome measures

Primary outcome measure was the change in the WOMAC Index between baseline and 12 weeks[28,29]. The WOMAC has three subscales that measure pain (range 0–50), stiffness (range 0–20), and function (range 0–170) and can be summarized as Index; the validated German version was used[29]. Secondary outcomes were WOMAC subscales (pain, stiffness and function separately), a Pain Disability Index (PDI)[30], Numeric Rating Scales (NRS, 0 to 10) for additional questions on pain and quality of sleep (instead of Visual Analogue Scales (VAS) as written in the protocol publication), a Pain Experience Scale (SES)[31], health-related quality of life (Short Form-36 Health Survey, SF-36[32]), Profile of Mood States (POMS)[33], a 7-point Likert Scale for general health-related participant satisfaction, a participant diary for rescue medication use, and safety (adverse events and serious adverse events). Outcomes were assessed using participant questionnaires. All outcomes were assessed at baseline, 6 and 12 weeks, and 6 and 12 months. Study nurses handed out questionnaires and diaries at baseline (before randomization), week 6 and week 12, and asked participants to complete them and to return them in sealed envelopes. The 6-months and 12-months questionnaires and participants' diaries were mailed by the study office. Adverse events were assessed by trial personnel in a standardized way at each visit and were also documented by the participants at the end of week 6 and week 12. Participants documented their expectations for treatment outcome at baseline (Fig. 1).

Statistical analyses

This study was designed to have 80% power to detect a difference of 10 points improvement (change to baseline) on the WOMAC Index after 12 weeks between both groups (pooled standard deviation = 20, two sided t-test $\alpha = 0.05$). To achieve this, 64 participants per group were needed. By taking drop outs into account, we planned to include 74 participants per group. The primary analysis population was the intention-to-treat (ITT) population including all randomized participants, who provided baseline data for the primary outcome. The primary outcome was the change of

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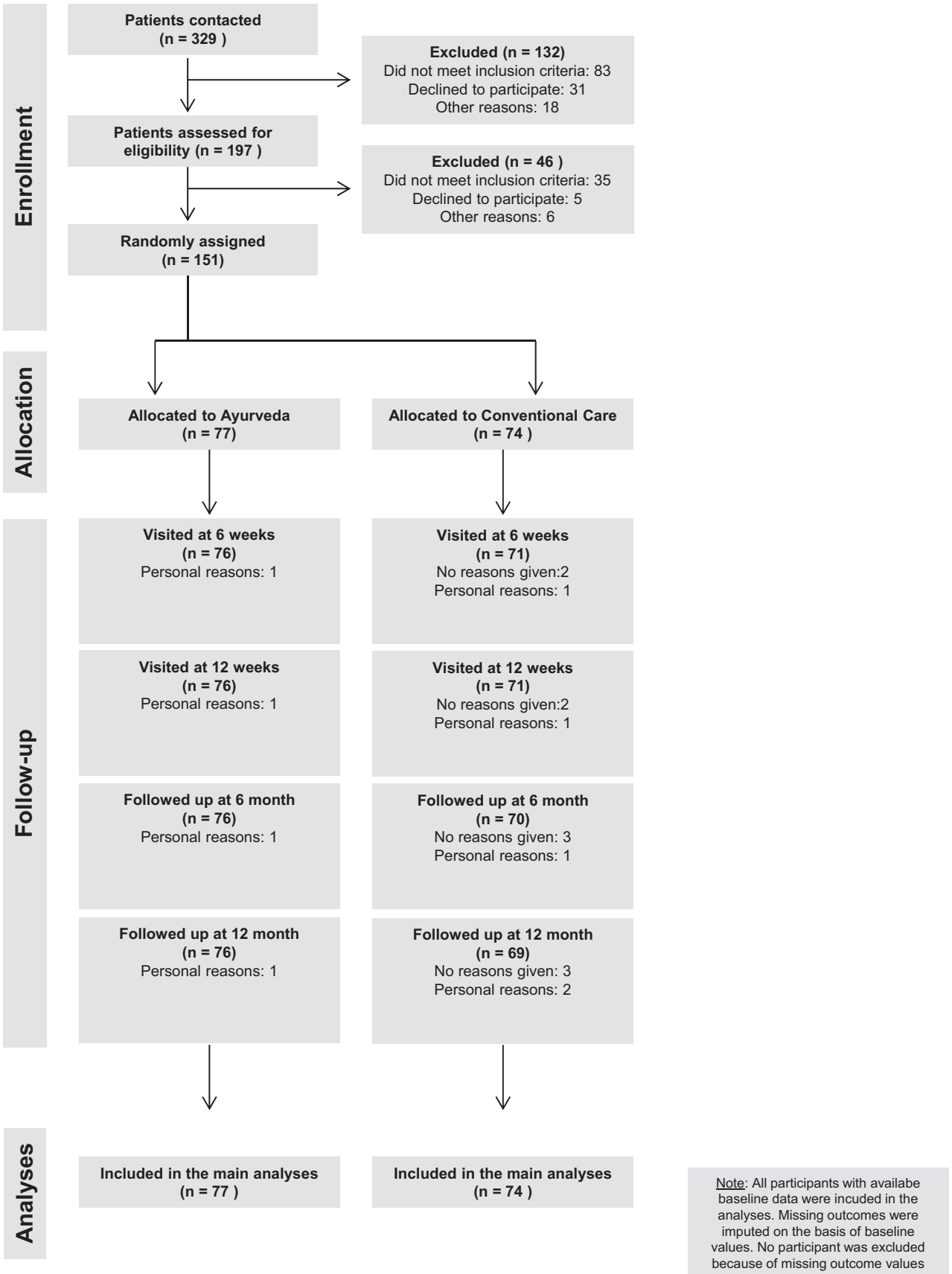

Fig. 2. Study flow diagram.

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the WOMAC Index after 12 weeks. Missing data were multiply imputed by maximum-likelihood based regression methods. Overall, 20 complete data sets were generated and combined adequately. Generalized Linear Mixed Models (GLM) were fitted to the data sets, including the treatment group as a fixed factor. Results are presented as adjusted WOMAC means per group with 95% confidence intervals and the two-sided p-value for the treatment group comparison. For sensitivity analysis ANCOVA models for WOMAC Index and WOMAC subscales were used after 12 weeks as independent variables. Treatment group and gender as fixed factors, baseline values and participants' expectations as linear covariates were applied to the data. The magnitude of effect sizes between and within groups for the primary endpoint was calculated using Cohen's d and its confidence intervals with $d > 0.5$ defining clinically relevant effect sizes[34]. Partial η^2, another measure of effect size, was used to measure the proportion of the total variance in the variable "WOMAC Index after 12 weeks" attributable to a particular independent variable (e.g., treatment group or expectation). Finally, within-group changes in both primary and secondary outcomes were assessed using univariate *t*-test statistics. Treatment responder analyses were performed using Chi–Square tests. We defined a decrease of at least 12 points as a treatment response for the main outcome parameter representing slightly stricter common response criteria[35]. All statistical analyses were carried out blind and prior to breaking the randomization code. Analyses were conducted using SPSS (release 23.0; IBM, Armonk, NY, USA, 2015).

Results

Between October 2010 and January 2014, 329 individuals were contacted by telephone, 197 were assessed for eligibility, and 151 were randomly assigned (77 to the Ayurveda group, 74 to the conventional group). Participants were treated between November 2010 and January 2015 and included into the primary analyses (Fig. 2). Four participants had missing values for all outcomes at 6 and 12 weeks, five participants at 6 months and six participants at 12 months; missing values were multiply imputed.

Overall, baseline characteristics were comparable between the groups (Table I). Participants in the Ayurveda group started with slightly lower mean WOMAC Index values. Participants and physicians had higher expectations for Ayurveda than for conventional care (Table I), which was considered in the sensitivity analyses.

The average number of treatment sessions was 13.5 ± 1.7 for Ayurveda participants and 14.0 ± 2.7 for conventional participants. Mean treatment duration time was 67.8 ± 4.1 min (90.2 ± 5.8 min in the Ayurveda group and 45.3 ± 2.5 min in the conventional group).

Primary outcome

Changes of the WOMAC Index from baseline to 12 weeks were more pronounced in the Ayurveda group (mean difference 61.0 [95% CI: 52.4;69.6]) than in the conventional group (mean difference 32.0 [95% CI: 21.4;42.6]) resulting in a significant group difference ($p < 0.001$) and a clinically relevant effect size (Cohen's d 0.68 [95% CI: 0.35;1.01] respectively partial $\eta^2 = 0.212$) (Table II). The between-group difference for the WOMAC Index persisted in similar magnitude up to the 12-month follow-up (Table II, Fig. 3).

The proportion of treatment responders was 93.5 % for Ayurveda, and 60.8% for conventional guideline care (Chi–Square: 21.24; $p < 0.001$).

Secondary outcomes

Changes within each subscale of WOMAC and all other secondary outcomes were also more prominent in the Ayurveda group at week 12. Similar findings were observed at months 6 and 12, with the exception of POMS scales and the mental component subscale of the SF-36 (Tables II and III).

In the first 12 weeks, the proportion of participants that used rescue pain medication was 18.9 % in the Ayurveda group, and 81.1% in the conventional group (Table IV).

Sensitivity analyses

The results were significantly sensitive to participant expectations and WOMAC baseline values. For all WOMAC subscales baseline values revealed a statistically significant influence ($p < 0.001$) on the primary outcome. Moreover, participant expectation significantly influenced the WOMAC subscales "function" ($p = 0.038$) and "stiffness" ($p = 0.034$) while no significant influence of participant expectation was observed for the subscale "pain" ($p = 0.149$). Respectively, for the global WOMAC index a significant influence of participant expectation ($p < 0.044$) was given. However, findings were very robust for sensitivity analyses (ANCOVA-modeled): the same significant differences between the two randomized groups ($p < 0.001$) for both the WOMAC Index (composite score of three WOMAC subscales) and for each single WOMAC subscale were observed in the treatment expectation-adjusted model. Expectation with respect to Ayurveda accounted for 2.6% and with respect to conventional care for 1.6% of the total variance in the adjusted model (see Table V for details).

Safety

There were 137 adverse events throughout the intervention period in 73 participants (59.7 % of participants [n = 46] in the Ayurveda group and 36.5 % [n = 27] in the conventional group had ≥ 1 adverse events). Ayurveda participants had a mean of 1.2 ± 1.3 adverse events (range 0–6), conventional participants 0.6 ± 1.0 adverse events (range 0–5). Both the difference in proportion ($p = 0.004$) as well as in the amount of adverse events ($p = 0.002$) were statistically higher in the Ayurveda group. Adverse events were related to the locomotor system (n = 88), the skin (n = 9) or to other reasons (n = 40). None of the intervention-related adverse events led to clinically relevant disease or required hospital treatment. A total of 4 serious adverse events occurred among 4 participants (fracture of radius, cholecystectomy, major depression episode, erysipelas; Ayurveda n = 3, conventional n = 1); none of the serious adverse events were classified as intervention-related.

Discussion

With this clinical trial we aimed to evaluate the effectiveness of an Ayurveda-medicine treatment approach in knee OA. After 12 weeks Ayurveda treatment led to a significantly greater and clinically relevant improvement of knee OA related complaints compared to the conventional guideline-based care with group differences maintained over 12 months.

This RCT is the first to evaluate the effectiveness of a complex multi-modal Ayurveda-medicine approach. We performed a head-to-head comparison with multi-modal complex conventional care. The Ayurvedic treatment approach and the conventional care were carefully designed with the aim of best practice for each group and including an individual diagnosis as basis for the treatment in the Ayurveda study arm. The multi-modal Ayurveda treatment was developed in a Delphi procedure before being put into practice[24]. As this trial was implemented in Germany, Western standards of care and the availability of Ayurvedic interventions in Europe were considered, including cultural, infrastructural and legal aspects into

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Table I
Baseline characteristics

Characteristic	All participants (n = 151)	Ayurveda (n = 77)	Conventional (n = 74)	*P*-value
Mean age (SD), years	61.2 (6.6)	60.9 (6.5)	61.5 (6.6)	0.562
Gender, n (%)				0.554
Male	35 (23.2)	18 (23.4)	17 (23.0)	
Female	116 (76.8)	59 (76.6)	57 (77.0)	
Mean body mass index (SD), kg/m^2	26.1 (3.9)	25.8 (3.7)	26.4 (4.2)	0.353
>10 years of school, n (%)	81 (54.4)	42 (56.0)	39 (52.7)	0.949
Mean duration of knee pain (SD), years	9.4 (8.1)	9.7 (9.1)	9.0 (7.0)	0.598
Consulting physicians due to knee OA, n (%)*				0.938
General practitioner	87 (57.6)	47 (61.0)	40 (54.1)	
Orthopedic surgeon	150 (99.3)	77 (100)	73 (98.6)	
Other surgeon	68 (45.0)	32 (41.6)	36 (48.6)	
Radiologist	128 (84.8)	67 (87.0)	61 (82.4)	
Neurologist	10 (6.6)	7 (9.1)	3 (4.1)	
Other physicians	31 (20.5)	17 (22.1)	14 (18.9)	
Participants with concomitant diagnoses (CD), n (%)	140 (92.7)	71 (92.2)	69 (93.2)	0.943
Mean number of CD (SD)	4.3 (2.5)	4.4 (2.6)	4.1 (2.4)	0.463
Participants with 1–2 CD, n (%)	27 (17.9)	13 (16.9)	14 (18.9)	
Participants with 3–4 CD, n (%)	48 (31.8)	22 (28.6)	26 (35.1)	0.917
Participants with ≥5 CD, n (%)	65 (43.0)	36 (46.8)	29 (39.2)	
Medication intake for knee OA	73 (48.3)	34 (44.2)	39 (52.7)	0.240
Mean systolic blood pressure (SD), mm Hg	139.4 (16.8)	137.3 (16.1)	141.5 (17.3)	0.124
Mean diastolic blood pressure (SD), mm Hg	85.6 (9.4)	84.1 (9.6)	87.1 (9.1)	0.047
Mean VAS score for knee pain (SD), mm	57.7 (11.7)	56.9 (11.7)	58.6 (11.7)	0.373
WOMAC, mean (SD)				
Index	92.6 (42.2)	91.1 (40.3)	94.2 (44.4)	0.647
Pain subscale	19.3 (8.5)	19.0 (8.1)	19.6 (9.0)	0.651
Stiffness subscale	9.9 (4.7)	9.8 (4.7)	10.1 (4.7)	0.734
Function subscale	63.4 (31.8)	62.3 (30.6)	64.5 (33.1)	0.662
PDI, mean (SD)	23.8 (11.4)	22.6 (10.6)	25.1 (12.1)	0.192
SES, mean (SD)				
Affective	27.1 (8.2)	27.3 (8.8)	26.9 (7.6)	0.743
Sensory	18.2 (5.7)	18.3 (5.6)	18.1 (5.8)	0.824
POMS, mean (SD)				
Depression factor	1.5 (0.9)	1.5 (1.0)	1.4 (0.9)	0.842
Fatigue factor	1.8 (0.9)	1.8 (0.9)	1.8 (0.9)	0.888
Vigor factor	2.0 (0.7)	2.0 (0.6)	2.0 (0.7)	0.989
Anger factor	1.7 (0.9)	1.8 (0.9)	1.7 (0.8)	0.309
SF-36, mean (SD)				
Physical component summary	33.2 (7.7)	33.4 (7.4)	33.0 (8.1)	0.752
Mental component summary	51.3 (11.3)	50.4 (12.1)	52.3 (10.5)	0.300
NRS (11-point 0–10), mean (SD)				
Pain at rest	3.4 (2.3)	3.4 (2.3)	3.4 (2.3)	0.970
Pain during movement	5.6 (1.9)	5.4 (2.0)	5.9 (1.7)	0.051
Everyday bothersomeness through pain	5.3 (2.0)	5.1 (2.1)	5.6 (1.9)	0.194
Sleep quality	5.6 (2.5)	5.2 (2.5)	6.0 (2.5)	0.067
Likert scales (7-point, 0–6), mean (SD)				
Participant's expectations of Ayurveda therapy				
Reduction of OA complaints	4.8 (1.1)	4.8 (1.1)	4.8 (1.0)	0.667
Overall effectiveness	4.7 (1.2)	4.6 (1.2)	4.9 (1.1)	0.111
Comprehensibility	4.6 (1.3)	4.6 (1.3)	4.6 (1.3)	0.862
Participant's expectations of conventional therapy				
Reduction of OA complaints	3.8 (1.3)	3.7 (1.3)	3.9 (1.4)	0.364
Overall effectiveness	3.7 (1.2)	3.4 (1.1)	4.0 (1.2)	0.002
Comprehensibleness	4.1 (1.4)	4.0 (1.3)	4.2 (1.4)	0.363
Physician's expectations of Ayurveda therapy				
Reduction of OA complaints	5.0 (1.0)	5.1 (1.0)	5.0 (1.0)	0.613
Overall effectiveness	4.5 (0.9)	4.5 (1.0)	4.5 (0.9)	1.000
Comprehensibility	4.7 (1.1)	4.7 (1.1)	4.7 (1.0)	1.000
Physician's expectations of conventional therapy				
Reduction of OA complaints	3.5 (0.9)	3.4 (1.0)	3.5 (0.8)	0.500
Overall effectiveness	3.0 (0.9)	3.0 (0.9)	3.0 (0.8)	1.000
Comprehensibility	3.8 (1.1)	3.7 (1.1)	3.8 (1.1)	0.577
Study center, n (%)				0.933
Study center 1	121 (80.1)	61 (40.4)	0 (39.7)	
Study center 2	30 (19.9)	16 (10.6)	14 (9.3)	

Abbreviations: SD = standard deviation; CD = concomitant disease; OA = osteoarthritis; WOMAC = Western Ontario and McMaster University Osteoarthritis Index; PDI = Pain disability index; SES = Pain experience scale; POMS = Profile of mood states; SF-36 = Short form 36; NRS = Numeric rating scale.
* Multiple answers possible.

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Table II
WOMAC index and WOMAC subscales

	Time Point				Within group differences (Baseline-week 12)			Between group differences (Baseline-week 12)	
	Week 6 mean (95% CI)	Week 12 mean (95% CI)	Month 6 mean (95% CI)	Month 12 mean (95% CI)	Δ mean (95% CI)	Effect Size [CI]	P-Value	Effect size [CI]	P-Value
WOMAC Index									
Ayur.	49.6 (41.9; 57.3)	30.0 (24.0; 36.1)	36.3 (28.1; 44.4)	43.0 (34.3; 51.7)	61.0 (52.4; 69.6)	1.78 [1.41;2.16]	<0.001	0.68 [0.35;1.01]	<0.001
Conv.	74.5 (65.7; 83.3)	62.2 (52.4; 72.0)	66.3 (56.9; 75.7)	69.6 (59.9;79.2)	32.0 (21.4; 42.6)	0.73 [0.46;1.00]	<0.001		
Pain									
Ayur.	10.4 (8.8; 12.0)	6.2 (4.8; 7.6)	7.2 (5.4; 8.9)	7.9 (6.3; 9.6)	12.8 (10.8; 14.8)	1.77 [1.37;2.17]	<0.001	0.64 [0.32;0.97]	<0.001
Conv.	15.9 (14.0; 17.9)	13.0 (10.7; 15.2)	13.7 (11.6; 15.8)	14.0 (11.9;16.1)	6.7 (4.4; 8.9)	0.70 [0.44;0.97]	<0.001		
Stiffness									
Ayur.	5.4 (4.4; 6.4)	3.6 (2.8;4.4)	4.1 (3.2; 4.9)	4.8 (3.8.; 5.8)	6.2 (5.2; 7.2)	1.51 [1.17;1.84]	<0.001	0.63 [0.30;0.95]	<0.001
Conv.	7.4 (6.4; 8.4)	6.7 (5.7;7.7)	6.8 (5.8; 7.8)	7.1 (6.0; 8.1)	3.4 (2.3; 4.4)	0.74 [0.47;1.00]	<0.001		
Function									
Ayur.	33.8 (28.2; 39.5)	20.2 (16.0;24.5)	25.0 (19.2; 30.8)	30.3 (23.8; 36.8)	42.0 (35.7; 48.4)	1.65 [1.29;2.00]	<0.001	0.64 [0.32;0.97]	<0.001
Conv.	51.2 (44.9; 57.5)	42.6 (35.6; 49.5)	45.8 (39.1; 52.5)	48.5 (41.5; 55.5)	22.0 (14.3; 29.7)	0.69 [0.42;0.96]	<0.001		

Abbreviations: WOMAC = Western Ontario and McMaster University Osteoarthritis Index; CI = Confidence Interval; Ayur. = Ayurveda Group; Conv. = Conventional Group.

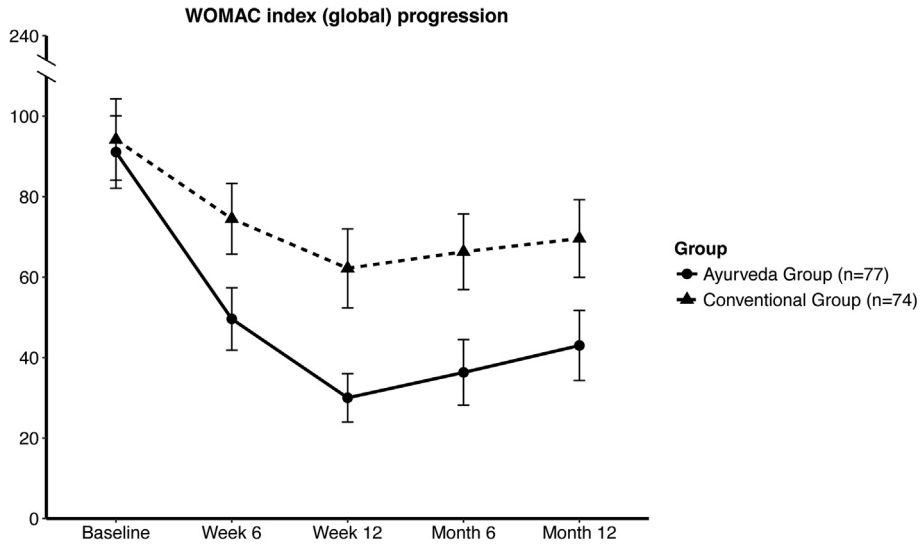

Fig. 3. WOMAC Index progression: baseline - 12 months.

the trial methodology. To ensure comparable individualized conventional treatments, the conventional intervention was guideline-based and developed in an evidence-based consensus procedure by the study team and two board-certified external orthopedic surgeons[15,16,26,27].

Notably, in the Ayurveda group physical and mental outcomes improved during the intervention, whereas afterwards mental improvements decreased again, but physical improvements maintained. Ayurveda represents a rather new therapy in Western countries. This was an open label study in which both care providers and participants were aware of the treatment being given, and participants had higher expectations for Ayurveda treatment compared to conventional care. Expectation is discussed as a prominent aspect of the placebo effect[36,37]. Research on a relatively Ayurvedic-naïve German population may introduce expectation bias; however, we controlled for expectations in the sensitivity analyses for this reason. While the unblinded nature formally remains a weak spot, blinding would have been not feasible, given the characteristics of the complex multi-modality Ayurvedic interventions.

Nevertheless, one might argue that the main part of the difference between groups might be solely due to non-specific effects in the Ayurveda group. Complementary medicine methods are well known to have non-specific effects of relevant size; as expectation is the main mechanism of the placebo effect, results of this study have been controlled for expectation in the analyses[38]. Furthermore, when comparing OA with other pain conditions it seems to be less sensitive to placebo effects as responder analyzes from sham-controlled acupuncture trials suggest[39]. To summarize, we believe that the open-label design introduced some non-specific effects; however, this does not appear to explain the magnitude of the effects that we observed.

Also, compared to data from other studies on the effectiveness of non-surgical approaches our conventional group showed similar effect sizes, while our Ayurveda group had larger effects[40,41].

It is interesting to see that while the intervention lasted 12 weeks only, beneficial effects persisted up to 12 months. In the Ayurveda group this might have been particularly due to the integration of elements of active self-care into the individualized therapeutic schemes, including self-empowerment via nutritional

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Table III
Secondary outcomes

	Ayurveda group (95% CI)				Conventional group (95% CI)				Between groups Baseline-week 12	
	Week 6	Week 12	Month 6	Month 12	Week 6	Week 12	Month 6	Month 12	Mean Δ (95% CI)	P-Value
PDI	14.1 (12.2; 16.1)	8.2 (6.7; 9.7)	9.8 (7.8; 11.9)	11.8 (9,4; 14,2)	20.3 (17.7; 22.9)	16.4 (13.9; 18.9)	17.2 (15.1; 19.4)	18.2 (15.6; 20.9)	5.8 (2.1; 9.5)	0.002
SES										
Affective	21.9 (20.1; 23.7)	18.3 (16.9; 19.8)	18.7 (17.1; 20.4)	19.0 (17.7; 20.3)	23.9 (22.3; 25.5)	21.5 (19.8; 23.2)	21.8 (20.2; 23.3)	21.2 (19.8; 22.6)	3.6 (1.0; 6.2)	0.007
Sensory	15.7 (14.7; 16.7)	13.5 (12.4; 14.5)	13.6 (12.5; 14.8)	14.2 (13.0; 15.4)	15.8 (14.8; 16.9)	15.0 (14.0; 16.1)	15.2 (14.2; 16.2)	15.3 (14.3; 16.3)	1.8 (−0.1; 3.7)	0.060
POMS										
Depress.	1.1 (1.0; 1.3)	1.1 (0.9; 1.3)	1.3 (1.1; 1.6)	1.5 (1.2; 1.7)	1.4 (1.1; 1.6)	1.2 (1.0; 1.4)	1.4 (1.2; 1.6)	1.3 (1.1; 1.5)	0.2 (−0.1; 0.4)	0.190
Fatigue	1.6 (1.4; 1.8)	1.5 (1.3; 1.7)	1.7 (1.5; 1.9)	1.9 (1.6; 2.1)	1.9 (1.7; 2.1)	1.7 (1.5; 1.9)	1.8 (1.6; 2.0)	1.8 (1.6; 2.0)	0.2 (0.0; 0.5)	0.089
Vigor	1.8 (1.7; 2.0)	1.8 (1.7; 2.0)	1.9 (1.8; 2.1)	2.0 (1.9; 2.2)	1.9 (1.8; 2.1)	1.9 (1.8; 2.0)	1.9 (1.7; 2.0)	2.0 (1.8; 2.1)	0.1 (−0.1; 0.3)	0.502
Anger	1.6 (1.5; 1.8)	1.5 (1.4; 1.7)	1.7 (1.5; 2.0)	1.7 (1.5; 1.9)	1.5 (1.3; 1.7)	1.6 (1.4; 1.7)	1.6 (1.5; 1.8)	1.7 (1.5; 1.9)	0.2 (−0.1; 0.4)	0. 217
SF-36 Subscales										
PCS	39.5 (37.7; 41.4)	44.9 (43.1; 46.7)	43.0 (40.9; 45,2)	41.7 (39.5; 44.0)	36.1 (34.1; 38.1)	37.9 (35.7; 40.1)	37.1 (35.0; 39.2)	37.1 (35.0; 39.1)	−6.6 (−9.3; −3.9)	<0.001
MCS	52.8 (50.5; 55.0)	53.7 (51.7; 55.7)	53.0 (51,1; 55,0)	52.5 (50.5; 54.4)	52.7 (50.1; 55.3)	53.9 (51.7; 56.1)	54.1 (52.0; 56.1)	54.0 (51.7; 56.2)	−1.7 (−5.1; 1.6)	0.308
NRS (11-p)										
Pain rest	1.7 (1.3; 2.1)	1.0 (0.7; 1.3)	1.2 (0.8; 1.5)	1.3 (1.0; 1.7)	2.5 (2.1; 2.9)	2.3 (1.7; 2.8)	2.2 (1.7; 2.6)	2.1 (1.7; 2.5)	1.3 (0.5; 2.0)	0.001
Pain mov.	3.4 (3.0; 3.9)	2.5 (2.0; 2.9)	2.6 (2.1; 3.0)	2.7 (2.2; 3.2)	4.7 (4.2; 5.1)	3.9 (3.4; 4.5)	4.0 (3.5; 4.5)	4.2 (3.7; 4.7)	0.9 (0.2; 1.6)	0.018
Pain both.	3.2 (2.8; 3.7)	2.0 (1.6; 2.3)	2.4 (1.9; 2.8)	2.5 (2.0; 3.0)	4.5 (4.0; 5.0)	3.8 (3.2; 4.4)	3.8 (3.3; 4.3)	4.1 (3.6; 4.7)	1.4 (0.7;2.1)	<0.001
Sleep	6.0 (5.5; 6.6)	6.4 (5.8; 7.0)	6.4 (5.8; 7.0)	6.0 (5.4; 6.5)	5.8 (5.2; 6.3)	6.5 (6.0; 7.1)	5.8 (5.2; 6.3)	6.0 (5.4; 6.6)	−0.6 (−1.5;0.2)	0.146

Abbreviations: CI = Confidence Interval; PDI = Pain disability index; SES = Pain experience scale; POMS = Profile of mood states; SF-36 = Short form 36; NRS = Numeric rating scale.

Table IV
Rescue medication use during the 12-week intervention period

Rescue medication (RM) category	Total number of RM intakes	Number of RM intakes in the Ayurveda group	Number of RM intakes in the conventional group
Category 1: NSAIDs oral	676	91	585
Category 2: NSAIDs topical	32	30	1
Category 3: other oral analgetics	32	24	8
Category 4: Paracetamol oral	67	7	60
	806 (100%)	152 (18.9%)	654 (81.1%)

Table V
ANCOVA interaction analyses

	WOMAC-Index		WOMAC Pain		WOMAC Stiffness		WOMAC Function	
	F	*P*-value	F	*P*-value	F	*P*-value	F	*P*-value
Corrected Model	14.835	<0.001	11.434	<0.001	15.088	<0.001	14.999	<0.001
Intercept*	8.225	0.005	5.115	0.025	7.937	0.006	8.890	0.003
Participant expectation	4.139	0.044	2.104	0.149	4.589	0.034	4.370	0.038
Baseline value	29.884	<0.001	21.734	<0.001	38.010	<0.001	31.881	<0.001
Group	23.859	<0.001	22.083	<0.001	17.104	<0.001	22.548	<0.001
Gender	1.387	0.241	2.214	0.139	0.441	0.507	1.113	0.293
Group* Gender	0.061	0.805	0.615	0.434	0.015	0.903	0.011	0.917

* The value of the dependent variable if all other explanatory variables hypothetically took on the value zero.

advice, lifestyle counseling and knee yoga postures, outlasting the 12-week intervention period.

A number of limitations apply to this study. One of them is the exclusion of individuals with obesity ≥ WHO grade II; however this played a minor role, since less than 5 individuals were excluded due to this criterion during the screening process.

Moreover, no comparison with intra-articular corticosteroids was done, since in Germany many patients refuse this treatment; being aware that our approach thus reduces generalizability to other countries, we excluded them with the aim of reducing selection bias[14]. Furthermore, the medication dosage was adapted to reduce the risk of side effects such as gastrointestinal bleeding.

The consultation duration differed between the groups. However, this reflects the usual care setting of both systems: reducing time in the Ayurveda group would not have allowed adequate treatment while increasing conventional treatment time would have introduced artificial settings[14].

In conventional care, patients not responding well to treatment often become interested in complementary and alternative medicine. This could have introduced bias towards Ayurveda. One method to reduce this bias could have been to recruit only incident cases of knee OA. However, in turn this also would have introduced an artificial setting, since Ayurveda is not seen as first line treatment.

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For ethical reasons Ayurveda participants were allowed to take conventional rescue medication. Because of this we decided to follow a superiority and not a non-inferiority or equivalence hypothesis. However, only 19% in the Ayurveda group compared to 81% in the conventional group used pain medication, suggesting that Ayurveda might be an option to reduce pain medication.

In this study the botanical/herbal medical options of Ayurveda medicine suggested for treatment of osteoarthritis could not be fully explored due to legal restrictions in Germany, while Ayurvedic safety aspects remain controversial[42]. Despite this, the inclusion of a full-fledged botanical treatment could have led to even more pronounced effects; In a preceding review and meta-analysis we identified 33 trials evaluating the use of Ayurveda for OA[13], most of them had methodological limitations. In contrast to our study[14], no previous trial used multi-modal treatment, although such an approach reflects routine practice in Ayurvedic care. Most trials evaluated standardized interventions with single botanicals. A RCT on rheumatoid arthritis demonstrated that individualizing Ayurvedic botanicals can be incorporated in RCTs[43].

Also, the authors were limited in providing information to the readers on how Ayurvedic treatment was individualized for participants with varying severity of knee osteoarthritis and body constitution. The authors realize that this information is of importance in replicating the results of the study to some extent. However, the authors plan to provide additional information on how treatments were individualized in a separate case-publication with teachable cases from this RCT.

The study design could serve as a blueprint for future trials on whole medical systems. Since several questions remain unanswered, particularly related to cultural transmigration of Ayurveda and economic aspects of complex Ayurveda interventions, future research should address qualitative analyses, health economic aspects and interdisciplinary approaches in addition to well planned RCTs in order to further prove the effectiveness of Ayurvedic medicine.

Conclusions

Results showed that Ayurveda led to significant and clinically relevant improvements in disease-specific symptom-reduction after 12 weeks of treatment compared with conventional care with most effects lasting over 12 months. However, further studies should be conducted to confirm the magnitude of the effect and to clarify the role of the different treatment components and of non-specific effects. The individualized Ayurvedic approach might contribute to more integrative and personalized OA care.

Author contributions

CW, AM, AntM, SG and CK conceptualized the research project, developed the methodology and the trial protocol. CW, AM, AntM took part in the acquisition of the financial support for the project leading to this publication. CW and AM conducted the investigation process; CK and AM coordinated the research activity planning and execution. CK, CW and AM wrote the initial draft of the manuscript. TO performed the formal statistical analysis. KD, AK, MM and ES took part in the development of the Ayurvedic treatment protocol and participated in writing and editing the manuscript. KI was responsible for the trial database software; KI and MS performed data entry and data curation and also took part in editing the manuscript.

Competing interests

Dr. Kessler reports personal fees from Bruno Zimmer, Germany, outside the submitted work. All other authors declare that they have no conflicts of interest: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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Transparency declaration

A. Michalsen and C.M. Witt had full access to all of the data in the study and take full responsibility for the integrity of the data and the accuracy of the data analysis. They affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Funding statement and role of the funding source

The study was supported by a grant from the Ministry of AYUSH, Government of India, Central Council for Research in Ayurvedic Sciences (CCRAS), Delhi, India, that had suggested a randomized trial including a conventional control group for knee OA. (Memorandum of understanding dated February 2, 2010); no other funding sources were used. All other decisions on design; data collection, analysis, and interpretation; and publication were completely independent of the funding source.

Data sharing

The study protocol has been published[14], the German version is available on request. Statistical code: Available from T. Ostermann (e-mail: thomas.ostermann@uni-wh.de). Data set: Certain portions of the analytic data set are available to approved individuals through written agreements with the authors.

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Supplementary data

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