Osteoarthritis and Cartilage

OARSI OSTEOARTHRITIS RESEARCH SOCIETY INTERNATIONAL

Clinical Trial

Effectiveness, safety, and cost–utility of a knee brace in medial knee osteoarthritis: the ERGONOMIE randomized controlled trial

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ARTICLE INFO

SUMMARY

Objective: This pragmatic, multicenter, open-label, randomized controlled trial (RCT) aimed to compare the effectiveness, safety, and cost–utility of a custom-made knee brace versus usual care over 1 year in medial knee osteoarthritis (OA).

Design: 120 patients with medial knee OA (VAS pain at rest >40/100), classified as Kellgren–Lawrence grade II-IV, were randomized into two groups: ODRA plus usual care (ODRA group) and usual care alone (UCA group). The primary effectiveness outcome was the change in VAS pain between M0 and M12. Secondary outcomes included changes over 1 year in KOOS (function) and OAKHQOL (quality of life) scores. Drug consumption, compliance, safety of the knee brace, and cost–utility over 1 year were also assessed.

Results: The ODRA group was associated with a higher improvement in: VAS pain (adjusted mean difference of −11.8; 95% CI: −21.1 to −2.5); all KOOS subscales (pain: +8.8; 95% CI: 1.4–16.2); other symptoms (+10.4; 95% CI: 2.7–18); function in activities of daily living (+9.2; 95% CI: 1.1–17.2); function in sports and leisure (+12.3; 95% CI: 4.3–20.3); quality of life (+9.9; 95% CI: 0.9–15.9), OAKHQOL subscales (pain: +14.8; 95% CI: 5.0–24.6); and physical activities (+8.2; 95% CI: 0.6–15.8), and with a significant decrease in analgesics consumption at M12 compared with the UCA group. Despite localized side-effects, observance was good at M12 (median: 5.3 h/day). The ODRA group had a more than 85% chance of being cost-effective for a willingness-to-pay threshold of €45 000 per QALY.

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Conclusions: The ERGONOMIE RCT demonstrated significant clinical benefits of an unloader custom-made knee brace in terms of improvements in pain, function, and some aspects of quality of life over 1 year in medial knee OA, as well as its potential cost—utility from a societal perspective.

Introduction

Knee osteoarthritis (OA) is a common degenerative joint disease, and a major cause of pain and disability in adults[1]. The medial compartment of the tibiofemoral joint is particularly exposed and sensitive to mechanical constraints, resulting in overloading of the articular cartilage and premature degeneration[2,3].

As recently outlined by the European League Against Rheumatism (EULAR), the OsteoArthritis Research Society International (OARSI), and the American College of Rheumatology (ACR), the management of knee OA includes pharmacological (use of analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), and intra-articular steroid injections) and non-pharmacological treatments (aerobic exercise, muscle strength training, and health education for self-management)[4—6]. While unloader knee braces were initially recommended by OARSI, they have been withdrawn from the most recent OARSI guidelines because of inconclusive evidence regarding their symptomatic benefits[4]. Conversely, they were 'strongly recommended' in the up-to-date ACR guidelines[6], demonstrating an absence of consensus on the effect of knee braces in OA in addition to usual care.

The aim of a valgus knee brace in medial knee OA is to apply corrective forces on load distribution in order to decrease internal pressure on the medial tibiofemoral compartment. This could contribute to pain reduction and increase functional recovery[7,8]. However, in practice, these unloader knee braces are infrequently prescribed in primary care[9,10], especially because their use is often limited by localized side-effects or discomfort, potentially resulting in weak acceptability and orthosis withdrawal[10,11]. Although several controlled trials have investigated the symptomatic effects of knee bracing[12—14], a Cochrane review and systematic analysis highlighted the lack of good-quality evidence for the effects on pain and function[7,8,15]. Moreover, there is a paucity of data regarding health-related quality-of-life outcomes or medico-economic analyses, which are key outcome measures[16]. Therefore, there is a need for high-quality studies, such as randomized controlled trials (RCTs), to assess the effectiveness, safety, and medico-economic impact of orthoses on knee OA[17] in primary care.

The main objective of this multicenter, pragmatic randomized controlled trial (RCT) was to assess the effectiveness, safety, and cost—utility of a distraction-rotation, custom-made knee brace (ODRA — ®PROTEOR) used in addition to the usual care versus the usual care alone (UCA) over a period of 1 year in patients with symptomatic medial knee OA.

Methods

Study design and participants

The ERGONOMIE study was a phase-3 randomized open-label parallel-group trial conducted at seven French sites (private and public hospitals). The clinicians, assessors, and volunteers were not blinded. Patients with symptomatic medial knee OA were screened by general practitioners, rheumatologists, physical therapists, and orthopedic surgeons, and referred to one of the participating centers. None of the patients had used an unloader knee brace before inclusion, but previous use of a neoprene sleeve was tolerated.

The inclusion criteria for patients were as follows: aged >40 years old; diagnosed with medial compartment knee OA defined according to the ACR criteria (VAS pain at rest $\geq$ 40/100 in the medial compartment, with more severe pain in the medial compartment than in the lateral compartment), radiological stage II, III, or IV according to the Kellgren—Lawrence (KL) grading[18] established from X-rays taken in the previous 6 months; and no change in pharmacological treatment for at least 3 months. Patients had to be able to understand and complete the self-report questionnaires. Major exclusion criteria were: severe venous insufficiency or prior deep vein thrombosis in the lower limbs; acute inflammation of the knee; knee valgus; other significant rheumatic disease; or indication for total knee replacement according to the medical specialist consulted. All participants provided written informed consent.

The study protocol was approved by the local ethics committee and the French national agency for the safety of medical products and devices. The study was registered in May 2016 (clinical trials number NCT02765685), which was after the onset of patient enrollment in February 2015, since the systematic registration of French clinical trials only became mandatory in 2016.

Randomization

Patients were randomly assigned in a 1:1 ratio to receive the distraction-rotation knee brace in addition to usual care (ODRA group) or to receive usual care alone (UCA group). To maintain balance between groups, dynamic allocation was centrally managed using a minimization algorithm[19], relying on the following factors: center, age (<65 vs $\geq$ 65 years), sex, disease duration (<2 vs $\geq$ 2 years), body mass index (BMI; < 25 vs $\geq$ 25), past history of other osteoarticular diseases affecting the target knee (meniscus tears, ligament injuries, tendonitis, bursitis), and radiological severity at baseline (KL II or III vs KL IV).

Intervention

Patients from both groups received the usual standard care for knee OA, including pharmacological (such as NSAIDs, analgesics, steroid injections, intra-articular hyaluronic acid (IAHA) injections) and non-pharmacological treatments (physiotherapy, spa therapy, etc.).

Patients randomized to the ODRA group were fitted with an ODRA brace (®PROTEOR; Dijon, France). All orthotic adjustments were performed by a certified orthotist. Patients were told to wear the brace for at least 6 h a day, 5 days a week, and to remove it during periods of rest and when lying down. ODRA is a custom-made valgus-inducing knee brace designed with an innovative system of dynamic distraction and dynamic external rotation of the leg that shifts the center of the load towards the natural

intercondyle position, thus limiting overload of the medial compartment[20,21] (Fig. 1; Appendix – Part A).

Follow-up assessments

Follow-up assessments were performed using self-reported instruments (VAS pain, knee injury, and osteoarthritis outcome score (KOOS), and osteoarthritis knee-and-hip quality-of-life (OAKHQOL) questionnaires[22,23]) at baseline (M0) and at each follow-up visit (M6 and M12). Patients were told that they would join the ODRA or UCA group after all assessments performed at M0 in order to limit potential disappointment bias of not receiving the brace. Moreover, patients were given the opportunity to try the ODRA brace at the end the protocol.

Clinical follow-up was completed via phone calls every 2 months for 1 year to collect compliance and safety data for the brace (in the ODRA group), and healthcare consumption (for both groups). Patients were given a diary to complete, which was then used as support for the phone calls in order to limit recall bias. During phone calls, patients were asked to complete the EuroQol 5-Dimension questionnaire (EQ-5D-3L®), a validated, standardized instrument commonly used for medico-economic evaluation[24–26].

Outcome measures

Effectiveness was defined as the benefit of the knee bracing compared with routine clinical practice[27]. The primary outcome was the change in VAS pain (0–100, min–max) between M0 and M12. Secondary effectiveness outcomes were the changes in KOOS subscale scores (pain, other symptoms, function in activities of daily living, function in sport and leisure, and knee-related quality of life)[23] and OAKHQOL domain scores (OA-specific domains covering physical activities, mental health, social support, social activities, and pain)[22,28] between M0 and M12. For both questionnaires, scores were normalized to a scale from 0 (worst) to 100 (best). At M12, the proportion of patients who experienced a clinically relevant improvement (minimal clinically important differences; MCID)[29] was calculated for VAS pain, KOOS function in activities of daily living, and the five domains of the OAKHQOL questionnaire. The proportion of patients who reached the patient-acceptable symptomatic state (PASS)[30] was computed for VAS pain. The selected MCID and PASS thresholds are shown in Table A1 (Appendix – Part B)[29,31].

The safety of the knee brace was assessed according to the potential (local and/or general) number of adverse effects of wearing the brace, compiled from phone calls and follow-up consultations. Compliance was self-reported and assessed according to the mean time the brace was worn (number of days per week and hours per day) over 1 year. Healthcare consumption types included analgesics, NSAIDs, and steroid and IAHA injection.

A cost–utility approach was used to assess the efficiency of the ODRA brace. It was specifically assessed by calculating the cost per quality-adjusted life year (QALY), based on the EQ-5D-3L (Appendix – Part C)[32]. For both groups, direct medical costs were estimated from the data obtained during each phone call from the societal perspective (including medical consultations, physiotherapy sessions, spa therapy, imagery, surgery, pharmacological treatments, and devices (including ODRA) (Appendix – Part C and Table A5).

Sample size

We assumed an absolute reduction in VAS pain of 19.9 points out of 100 for the ODRA group (based on the MCID for knee OA[33]) and no reduction (0 points out of 100) for the UCA group. Based on a previous exploratory study[21], which showed an absolute reduction in pain (25 points ± 25.3) after 12 months in 20 knee OA patients wearing the ODRA brace, we increased the expected variability by setting the standard deviation (SD) at 30 for the ODRA group and 40 for the UCA group in order to take the heterogeneity of patient management in the UCA group into account. Based on these assumptions, with an alpha risk of 5% and a power of 80%, 51 patients were required per group. We planned to enroll 60 patients in each group in case patients were lost to follow-up.

Statistical analysis

At baseline, we compared the demographic (age, sex, body mass index (BMI), social deprivation using EPICES score, education level) and disease characteristics (OA disease duration, KL grading, OA treatments) between groups using chi-square tests for qualitative variables and Student's tests or non-parametric tests for continuous variables.

The outcome measures were described for each group using mean change from baseline to follow-up with 95% confidence intervals (CI). As specified in the protocol, the primary analysis was performed on complete data, with an intention-to-treat analysis under the assumption of maximum bias[34] for patients lost to follow-up (no change in pain in the ODRA group, reduction of 20 points in the UCA group), and adjusted for unbalanced factors between groups when there were differences at baseline ($P < 0.20$). Therefore, the main analysis included all patients with no missing data for adjustment variables under the maximum bias hypothesis. This was then completed by a full-set analysis (exclusion of patients with missing data on outcome). The change in VAS pain between baseline and each follow-up was analyzed separately using linear regression. The changes in the KOOS and OAKHQOL scores were

Fig. 1 Representation of the distraction–rotation mechanism of the ODRA brace (Laroche *et al.*, 2014; with permission).

analyzed using a mixed model adjusted for unbalanced baseline factors. Due to significant interactions between groups and time assessment, the changes in KOOS and OAKHQOL between baseline and each follow-up were analyzed separately using linear regression. The effect of ODRA vs UCA on the probability of reaching MCID for VAS pain and PASS was estimated using logistic regression models, which were run separately for M6 and M12.

Safety endpoints were described for all patients. Patients for whom compliance was available at least once in each period (M0–M6 and M6–M12) were considered for the compliance analysis. Among these patients, the median compliance with its interquartile range (IQR) was computed for the whole M0–M12 period. Healthcare consumption types were compared between groups using chi-square tests.

The cost–utility analysis was performed using the incremental cost-effectiveness ratio (ICER), calculated by dividing the incremental direct costs (difference in mean costs between the ODRA and UCA groups) by incremental QALY (difference in mean QALY). The main cost–utility analysis included patients with complete data. A complementary cost–utility analysis was performed using multiple imputation with adjustment for unbalanced baseline factors in order to take into account patients with missing data. The ICER was then compared with a reference value representing the maximum amount of investment (i.e., willingness-to-pay threshold) collectively accepted by society for one additional QALY. To our knowledge, there is no international or French consensus for the willingness-to-pay threshold for biomechanical devices in knee OA[16,35]. We therefore based our comparison on a threshold of almost €45 000 used in recent studies of other medical devices for knee OA[36,37]. We then constructed an acceptability curve based on 10,000 samples generated by a non-parametric bootstrap analysis of the differential costs and QALY observed for the two strategies (Appendix – Part C). Direct medical costs and QALY at 1 year were averaged for all patients. They were compared between groups using chi-square tests or non-parametric tests. Costs are presented in euros (€).

A two-sided *P*-value of less than 0.05 was considered significant. All analyses were performed with SAS 9.4. To facilitate understanding in the results and discussion, the results at M6 are only reported in the Appendix – Part B (Tables A2, A3, A4, and Fig.A1).

Results

Population characteristics

A total of 121 patients were enrolled between February 2015 and July 2016 (Fig. 2). One patient withdrew consent, leaving 120 knee OA patients included at baseline. Despite randomization, ODRA patients had a lower level of education, had more frequent prior history of knee surgery on the target knee, and higher VAS pain at baseline compared with UCA patients (Table I). The effectiveness results were adjusted for the following factors ($P < 0.20$): VAS pain at baseline, other osteoarticular disease affecting the target knee, prior history of surgery on the target knee, pain medication, socioprofessional category, and level of education.

Effectiveness

The main outcome was available for 54 of 60 patients (90%) in the UCA group and 49 of 60 patients (82%) in the ODRA group. The primary analysis revealed that the adjusted mean difference in VAS pain was higher in the ODRA group than in the UCA group, with an adjusted mean difference of −11.8 (95% CI: −21.1 to −2.5). Full-set analysis and the variation in VAS pain between M0 and M12 in each group are detailed in Table II.

The comparison between M0 and M12 revealed that ODRA patients exhibited significant improvements in all subscales of the KOOS, and in the pain and physical activities subscales of the OAKHQOL compared with the UCA group (Fig. 3). An interesting trend was found in the mental health domain of the OAKHQOL, suggesting an improvement in ODRA patients at M12.

MCID and PASS

Patients in the ODRA group were more likely to reach MCID at M12 for VAS pain (adjusted odds ratio (OR) = 2.76 [95% CI: 1.05–7.23]; $P = 0.04$), for KOOS function in activities of daily living (OR = 4.90 [95% CI: 1.68–14.32]; $P = 0.004$), and for three out of five domains of OAKHQOL: physical activity (OR = 4.43 [95% CI: 1.38–14.21]; $P = 0.01$), pain (OR = 3.56 [95% CI: 1.20–10.56]; $P = 0.02$), and mental health (OR = 2.91 [95% CI: 1.04–8.12]; $P = 0.04$; Table III). Likewise, the proportion of patients reaching the PASS for VAS pain was significantly higher in the ODRA group than in the UCA group (OR = 2.97 [95% CI: 1.09–8.10]; $P = 0.03$).

Compliance and safety

Between M0 and M12, the patients ($n = 47$) wore the ODRA brace for a median of 6 days per week (IQR: 5–6.75) and a median of 5.3 h per day (IQR 3.7–7).

51 patients in the ODRA group reported local side-effects, mainly skin irritation from rubbing against the brace ($n = 39$) and itching ($n = 27$). 15 patients reported moderate leg edema, and five mentioned the appearance or worsening of varicose veins. These side-effects led to 26 provisional and eight definitive withdrawals of the brace (16%), as well as adjustments of the brace by the local orthotist. One serious side-effect (deep vein thrombosis) potentially related to the orthosis was identified. One patient in the UCA group also had deep vein thrombosis during follow-up.

Healthcare consumption

Between M0 and M12, 28.3% of patients in the ODRA group had at least one acid hyaluronic injection, compared with 41.7% in the UCA group ($P = 0.13$). The proportion of patients using pharmacological treatments did not differ significantly between groups (Table IV). However, the median reduction in the number of analgesics used in the week preceding the consultation between M0 and M12 was −6.5 (IQR: 15–0) in the ODRA group vs 0 (IQR: −4 to 7) in the UCA group ($P < 0.001$). Non-pharmacological treatment (physiotherapy sessions or spa therapy) did not differ significantly between groups during follow-up. Otherwise, four patients (two in each group) underwent surgery for total knee replacement over the study period.

Cost–utility

The main cost–utility analysis was performed on 90 patients (40 from the ODRA group) because of missing data. The cumulative direct difference in cost over 1 year was €1335 (95% CI: 620–2049), with higher costs in the ODRA group than in the UCA group (€2116 vs €781, respectively; $P = 0.0002$), mainly due to the cost of the orthosis itself (€1200). The mean difference in QALY was 0.08 (95% CI: −0.003 to 0.16) (29 days) in favour of the ODRA group (QALY 0.70 vs 0.62; $P = 0.07$). The calculated ICER was €16 683 per additional QALY (95% CI: −32,929 to 42,808). A cost–utility acceptability curve suggested that ODRA could be cost-effective for 85% of the simulation at a threshold of €45 000 per QALY gained (Fig. 4).

Fig. 2 Flow chart of the ERGONOMIE RCT.
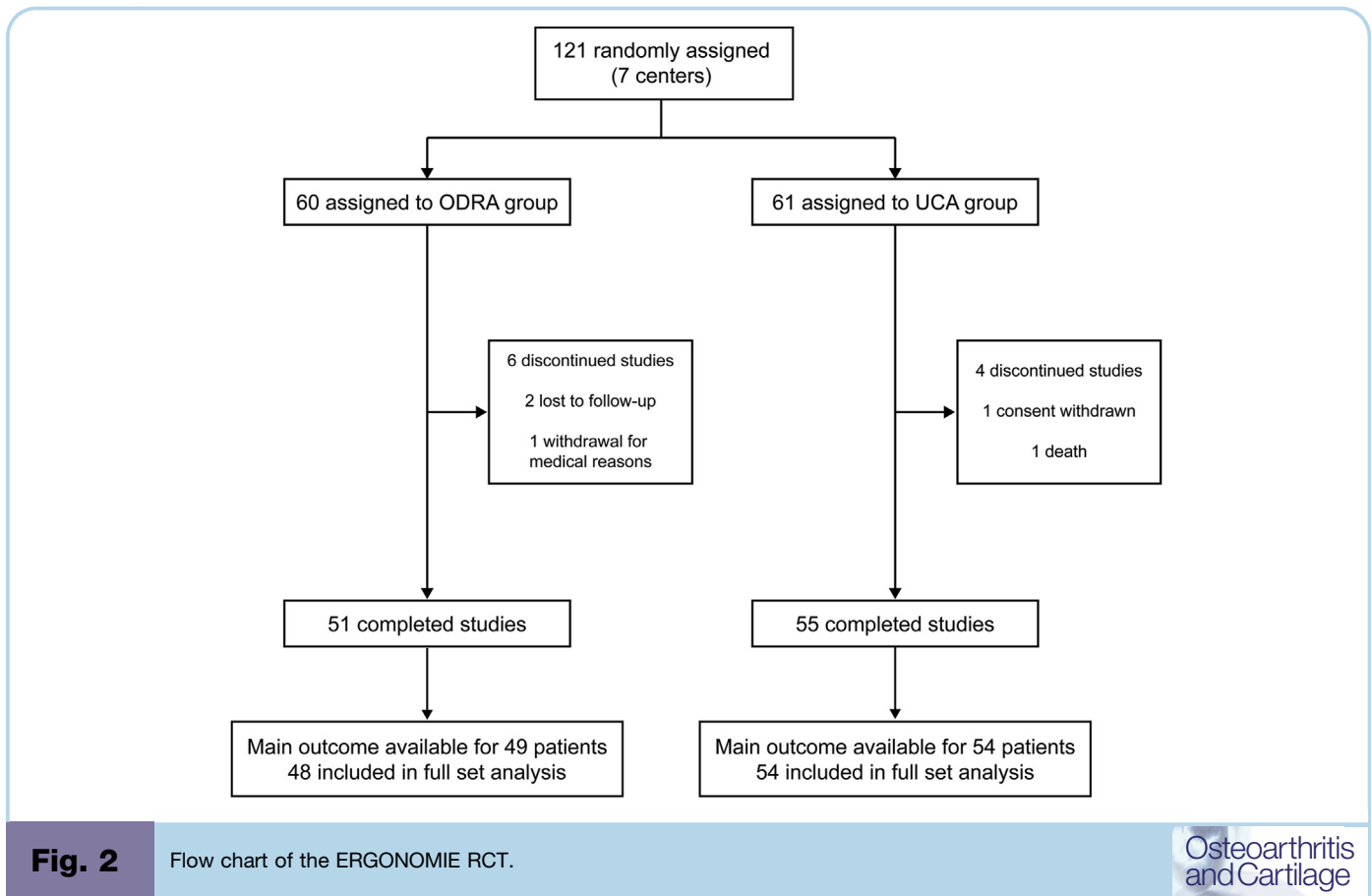
The results of the complementary cost−utility analysis revealed a slight increase in the ICER (ICER = €25 225; 95% CI: 23,129−45,331); Appendix − Table A6).

Discussion

To our knowledge, this is the first randomized controlled OA trial investigating the medium-term benefits of an unloader knee brace in terms of both clinical and economic outcomes, in a regular healthcare setting, with high external validity due to the relatively unselected patients and multidisciplinary screening. Thus, ERGO-NOMIE will be helpful in answering the question of whether this custom-made orthosis has additional value in real life. Our results demonstrated that the combination of an ODRA brace and usual care is statistically associated with improvements in pain, function, and some aspects of OA health-related quality of life at 1 year in comparison with usual care alone. They also confirmed the good safety profile of the unloader knee brace. Finally, the ODRA brace seems to be cost-effective, as suggested by the cost−utility analysis.

The main result of ERGONOMIE is the significant improvement in pain and function observed in the ODRA group when compared with the UCA group. These results are consistent with previous RCTs suggesting that additional treatment with an unloader knee brace improves pain and physical function[14,38,39] compared with usual care. In a study by Moyer et al.[11], these effects appeared smaller, but were still present when compared with a control orthosis group. In addition, dichotomous variables such as MCID and PASS are useful for algo-functional outcome measures, since

they specify the proportion of patients who 'feel better' and 'feel well', respectively[40]. In our study, the difference was clinically relevant because patients in the ODRA group 'felt better' in terms of mental health (OAKHQOL), function in activities of daily living (KOOS), and VAS pain, and 'felt well' for VAS pain, compared with patients in the UCA group.

Recently, Thoumie et al.[38] observed a similar improvement in short-term pain (−26/100 on VAS) with another valgus-inducing knee brace (three-point pressure) after a 6-week treatment period, showing that the knee brace provided immediate pain relief thanks to its biomechanical effect. Our results suggest that this positive effect, which is associated with significantly improved function and quality of life, could be extended to the medium-term without a decrease in symptomatic effects. In a comparable RCT including 130 knee OA patients, Brouwer et al.[12] observed no difference in pain, function (evaluated using the Hospital for Special Surgery score − HSS), or quality of life (evaluated by EQ-5D®) at 1 year. However, the HSS score is not as effective as the KOOS for assessing global function, as indicated by OARSI[41]. The KOOS includes the WOMAC (Western Ontario and McMaster Universities Arthritis Index) plus others items related to function in leisure and sport activities, and is therefore a better indicator of overall function in knee OA[23]. In our study, a significant improvement in all KOOS subscales was observed in the ODRA group, showing that global function had improved after 1 year. Ostrander et al.[42] observed a similar improvement in the KOOS scores of patients with an unloader brace over a shorter period. Furthermore, the EQ-5D® questionnaire used by Brouwer et al. is a

	ODRA group (n = 60)	UCA group (n = 60)	P-value
Socio-demographic characteristics			
Age (years; mean ± SD)	65 ± 11,8	62.2 ± 11,1	0.44
Women	34 (56.7%)	34 (56.7%)	1
BMI (kg/m^2; mean ± SD)	29.4 ± 5.2	29.8 ± 5.9	0.65
Education level			**0.01***
less than high school diploma degree	25 (44.6%)	13 (23.6%)	
High school diploma degree	16 (28.6%)	13 (23.6%)	
More than 2 years after high school diploma degree	15 (26.8%)	29 (52.7%)	
Type of occupation before retirement			0.14
Skilled	15 (25.4%)	22 (37.9%)	
Unskilled	34 (57.6%)	32 (55.2%)	
Unemployed	10 (17%)	4 (6.9%)	
Social deprivation (EPICES score ≥ 30)	19 (32.2%)	14 (24.1%)	0.33
Disease characteristics			
VAS pain 0—100 (mean ± SD)	61.8 ± 17.4	54.8 ± 50.1	**0.03***
Disease duration (years; median, IQR)	3.1 (1.2—9.8)	4.3 (1.0—6.7)	0.78
Radiological Kellgren—Lawrence grading			0.73
II	18 (30%)	15 (25%)	
III	31 (51.7%)	31 (51.7%)	
IV	11 (18.3%)	14 (23.3%)	
History of surgery on the target knee	26 (43.3%)	15 (25%)	**0.03***
Other osteoarticular disease affecting the target knee	2 (3.3%)	8 (13.3%)	**0.05***
OA treatment			
Within the previous 6 months			
Physiotherapy	18 (30%)	21 (35%)	0.56
Hyaluronic acid injection	21 (35%)	21 (35%)	1
Intra-articular steroid injection	17 (28.3%)	18 (30%)	0.84
Within the previous week			
Analgesics	46 (76.7%)	38 (63.3%)	0.11
NSAIDs	12 (20%)	14 (23.3%)	0.66

Data are n and % unless indicated.
SD: standard deviation.
NSAIDs: nonsteroidal anti-inflammatory drugs.
  * Statistical difference between groups was observed (P < 0.05).

Table I Baseline population characteristics (ERGONOMIE RCT)

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	Unadjusted mean change from baseline (95% CI)		*Adjusted between group difference (95% CI)	
	Full set analysis (n = 103)	**Maximal bias analysis (n = 120)**	**Full set analysis (n = 101)**	**Maximal bias analysis (n = 109)**
UCA	−9.4 (−16.4 to −2.4)	−10.4 (−16.8 to −4.1)	Reference	Reference
ODRA	−21.2 (−28.2 to −14,1)	−17.3 (−23.4 to −11.2)	−13.0 (−22.6 to −3.3)	−11.8 (−21.1 to −2.5)

For changes within group, a negative value indicates improvement.
For changes between groups, negative values favor ODRA.
Primary effectiveness analysis corresponds to maximal bias analysis.
UCA: usual care alone; CI: confidence interval.
  * Adjusted for VAS pain at baseline, other osteoarticular disease affecting the target knee, prior history of surgery on the target knee, pain medication, socio-professional category and level of education.

Table II Mean reduction in VAS pain between M0 and M12 (ERGONOMIE RCT)

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more generic instrument for measuring quality of life in terms of preferences associated with an individual's health state than OAKHQOL, which is a disease-specific instrument for OA of the lower limbs[22,23]. Specifically, our results showed that three OAKHQOL domains were clearly improved in the ODRA group (pain, physical activities, and mental health). The two other OAKHQOL domains (social support and social activities) might not be improved in the ODRA group because these domains are less sensitive to change[43] and rely more on the patient's environment than on a potential effect of the biomechanical device.

Patients in the ODRA group did report side-effects, including skin irritation or swelling[11]. However, given the good results in terms of
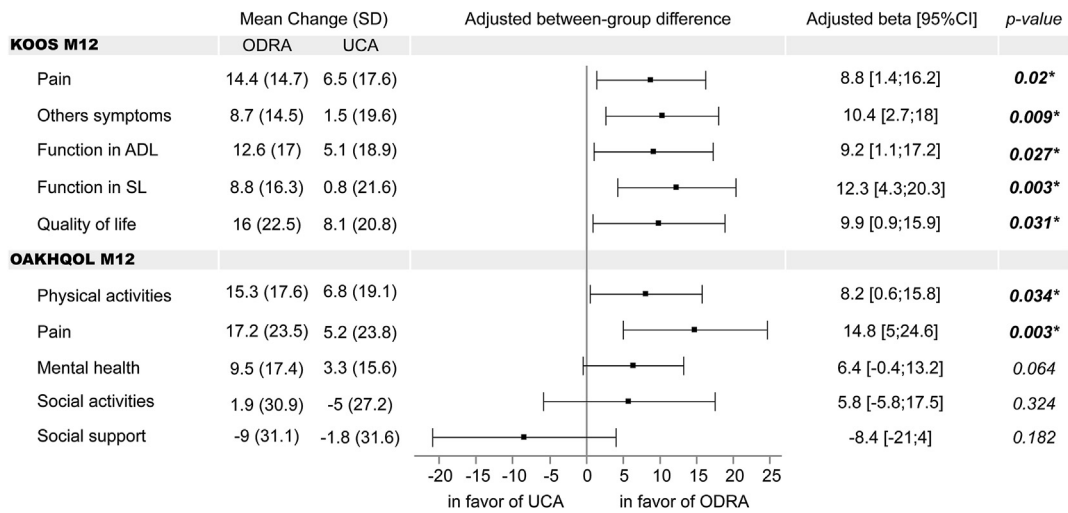
KOOS M12	Mean Change (SD)		Adjusted between-group difference	Adjusted beta [95%CI]	p-value
	ODRA	UCA			
Pain	14.4 (14.7)	6.5 (17.6)		8.8 [1.4;16.2]	0.02*
Others symptoms	8.7 (14.5)	1.5 (19.6)		10.4 [2.7;18]	0.009*
Function in ADL	12.6 (17)	5.1 (18.9)		9.2 [1.1;17.2]	0.027*
Function in SL	8.8 (16.3)	0.8 (21.6)		12.3 [4.3;20.3]	0.003*
Quality of life	16 (22.5)	8.1 (20.8)		9.9 [0.9;15.9]	0.031*
OAKHQOL M12					
Physical activities	15.3 (17.6)	6.8 (19.1)		8.2 [0.6;15.8]	0.034*
Pain	17.2 (23.5)	5.2 (23.8)		14.8 [5;24.6]	0.003*
Mental health	9.5 (17.4)	3.3 (15.6)		6.4 [-0.4;13.2]	0.064
Social activities	1.9 (30.9)	-5 (27.2)		5.8 [-5.8;17.5]	0.324
Social support	-9 (31.1)	-1.8 (31.6)		-8.4 [-21;4]	0.182

-20 -15 -10 -5 0 5 10 15 20 25
in favor of UCA   in favor of ODRA

Fig. 3 Evolution of KOOS and OAKHQOL scores between M0 and M12 in the ODRA group compared with the UCA group (ERGONOMIE RCT).

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	% of patients reaching MCID		Multivariate analysis (reference = UCA)	
	ODRA	UCA	ORa (95% CI)	P-value
VAS pain				
Pain reduction > 19.9 points	46.9	27.8	2.76 (1.05–7.23)	0.04*
KOOS				
Functional improvement in activities of daily living ≥ 9 points	58.1	29.2	4.90 (1.68–14.32)	0.004*
OAKHQOL				
Physical activity improvement ≥ 19 points	35.3	13.2	4.43 (1.38–14.21)	0.01*
Pain improvement ≥ 21.4 points	35.3	17	3.56 (1.20–10.56)	0.02*
Mental health improvement ≥ 11.7 points	39.2	18.9	2.91 (1.04–8.12)	0.04*
Social activity improvement ≥ 5.8 points	35.3	34	0.95 (0.37–2.44)	0.91
Social support reduction ≥ 18.2 points	11.8	20.8	0.53 (0.15–1.85)	0.32

MCID: minimal clinically important difference.
UCA: usual care alone.
VAS: visual analog scale.
KOOS: knee injury and the osteoarthritis outcome score.
OAKHQOL: osteoarthritis knee-and-hip quality-of-life questionnaire.
ORa: Odds ratio adjusted for VAS pain at baseline, other osteoarticular disease affecting the target knee, prior history of surgery on the target knee, pain medication, socio-professional category, and level of education.
* Statistical difference between groups was observed (P < 0.05).

Table III Proportion of patients who experienced significant relevant improvement (MCID) in effectiveness criteria between M0 and M12 in the ODRA group compared with the UCA group (ERGONOMIE RCT)

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acceptability and compliance, patients (even elderly ones) seemed to tolerate the ODRA brace well in the medium term. Indeed, the estimated percentage of patients who continued to use the ODRA brace daily at 1 year was particularly high (84%) compared with other studies[12,44,45]. This could be partly associated with the good clinical results of our study compared with the literature. In addition to its effectiveness, the ODRA is custom made and less bulky than the three-point orthosis currently prescribed for medial knee OA, which may improve tolerance and acceptability.

Our analysis of the consumption of analgesics and NSAIDs revealed some differences between the groups at M12. There was a significant decrease in the use of analgesics in the ODRA group, whereas NSAID consumption remained stable in the UCA group. There is almost no literature that focuses on this potential analgesic-sparing effect; only one previous RCT reported lower analgesic consumption at 6 weeks, but this was not statistically significant[38]. There was no significant reduction in the use of intra-

	ALL	ODRA	UCA	*P*-value
ANALGESICS				
N and % of patients using analgesics within the previous 7 days at M0	84 (70%)	46 (76.7%)	38 (63.3%)	0.11
N and % of patients using analgesics during the study period	98 (81.7%)	48 (80%)	50 (83.3%)	0.64
NSAIDs				
N and % of patients using NSAID within the previous 7 days at M0	27 (22.5%)	13 (21.7%)	14 (23.3%)	0.83
N and % of patients using NSAID during the study period	73 (60.8%)	35 (58.3%)	38 (63.3%)	0.57
HYALURONIC ACID INJECTION (targeted knee)				
N and % of patients with hyaluronic acid injection within the 6 months preceding M0	42 (35%)	21 (35%)	21 (35%)	1
N and % of patients with hyaluronic acid injection during the study period	42 (35%)	17 (28.3%)	25 (41%)	0.13
STEROID INJECTION (targeted knee)				
N and % of patients with steroid injection within the 6 months preceding M0	35 (29.2%)	17 (28.3%)	18 (30%)	0.84
N and % of patients with steroid injection during the study period	16 (13.3%)	10 (16.7%)	6 (10.1%)	0.28

NSAID: non-steroidal anti-inflammatory drug.

Table IV Comparison of symptomatic pharmacological treatment between groups at M0 and M12 (ERGONOMIE RCT)
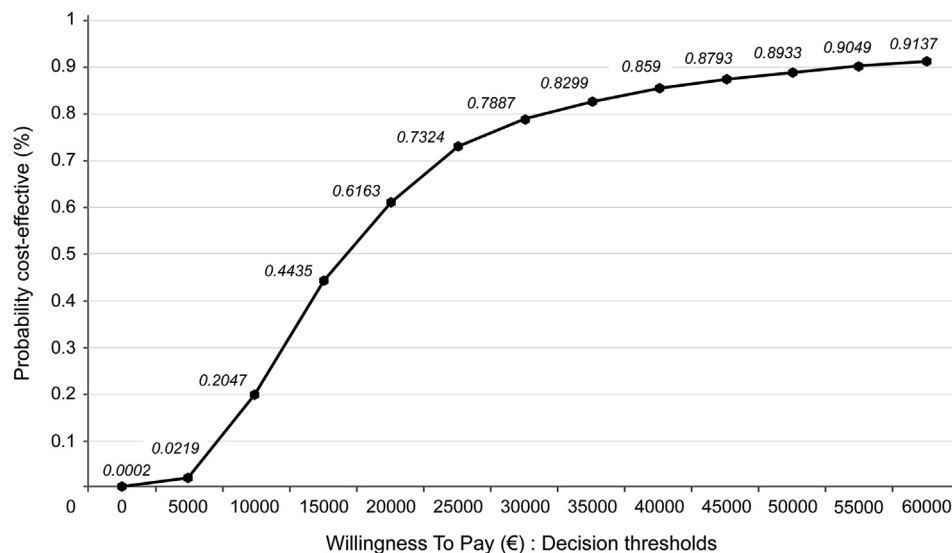

Fig. 4 Acceptability curve for the choice of strategy (ERGONOMIE RCT). This curve makes it possible to evaluate the probability that the ODRA strategy will be cost-effective according to several willingness-to-pay thresholds. It is based on the 10,000 samples generated by the bootstrap analysis. At each value of the willingness-to-pay threshold (***x***-axis), the curve gives the proportion of samples for which the ICER ratio is below this WTP value. This proportion (***y***-axis) reflects the probability for which the ODRA strategy is more efficient than the UCA strategy at the WTP value. To our knowledge, there is no consensus regarding thresholds for biomechanical devices in knee OA in France, unlike in other countries[16,34].

articular symptomatic treatments (steroid or IAHA injection) at M12 despite significant improvements in pain and quality of life.

Finally, the cost–utility analysis showed an annual direct cost of €781 per year for the UCA group. This is comparable to estimated costs in previous French studies on knee OA[37,46,47], keeping in mind that the extra costs in the ODRA group are mainly attributable to the price of the brace. The extra costs associated with one additional QALY gained with the ODRA brace varied between €16 683 and €25 225, which is comparable with the ICER previously reported for the treatment of knee OA (from €4000 to €57 550 and

from €240 to €53 225 for disease-modifying osteoarthritis drugs (DMOADs) and IAHA, respectively[36]). When we compare our ICER to the willingness-to-pay threshold of €45,000 suggested in the literature, the likelihood that the ODRA brace would be cost-effective is more than 85% compared with usual care alone. Concerning QALY, the incremental effectiveness of the ODRA (mean difference in QALY) is comparable with the literature (from 0.01 to 0.025 for DMOADS, and from 0.024 to 0.115 for IAHA[36]). Taken together, these results suggest that, from a societal perspective, the

ODRA would have a cost–utility that has not been demonstrated so far for a brace in knee OA.

We recognize that this pragmatic RCT had some limitations. Neither the investigators nor the participants were blinded to the treatment group. In trials evaluating knee braces, it is difficult to guarantee both the blinding of patients and of medical investigators[48]. The absence of a neutral orthosis as control group was also a limitation. However, a knee brace that does not realign may nonetheless have therapeutic effect by altering proprioceptive input, or muscle coactivation or recruitment, and may limit injurious joint motion, and thus not constitute a pure placebo. In RCTs focused on OA, a placebo response is not necessarily equivalent to the improvement of symptoms because this improvement could be related to natural variation of disease activity, regression to the mean, additional undeclared treatments, response bias, or the Hawthorne effect[49]. However, a placebo effect cannot be fully excluded. Moreover, as a reflection of the real-world setting and despite randomization, significant differences between groups were observed at baseline. Indeed, at the time of randomization, for some patients ($n = 3$) the investigators erroneously reported osteo-articular disease affecting the target knee, which was used in the minimization algorithm. The values were then corrected, but this may explain some imbalance between groups. However, these differences were at least partially balanced because we adjusted comparisons for these factors.

Another limitation was the declarative collection of healthcare consumption and direct medical costs, even if this was crossed with different sources (self-reported diary, follow-up visits, phone calls). This method was required because access to data via larger national medical databases, such as the French national health insurance inter-regime information system, was not authorized.

In conclusion, the ERGONOMIE study has shown that combining the ODRA brace with usual care is a promising therapeutic strategy, which demonstrates good acceptability and tolerance in patients with medial knee OA. Further research is needed to confirm the cost–utility of this expensive custom orthotic device, and to investigate the predictive factors of patient response, which would help clinicians to identify the best candidates for an ODRA brace. Longer-term studies over 2–5 years are also warranted to check long-term improvement, and to confirm the good safety profile and the OA-related real-life habits of patients fitted with this device. The potential impact of the ODRA on disease progression, cartilage damage, or knee-replacement surgery must also be considered because of its medico-economic and societal costs.

Conflicts of interest

All authors declare no conflict of interests and disclose no financial or personal relationships with other people or organizations that could inappropriately influence (bias) this work. The PROTEOR group had no role in the study design or performance, writing of the manuscript, or decision to publish.

Acknowledgements

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.joca.2020.11.009.

Author contributions

MG, CM, PO, and IF contributed to the design of the study. AD, EB, CB, AC, TC, DL, JMC, AR, JFM, KM, MT, and DW participated in the acquisition and inclusion of data. MG drafted the first version of the manuscript, contributed to the interpretation and discussion of the results, and coordinated the manuscript writing. IF and ALS performed the statistical analysis, and participated in the interpretation analysis and discussion of this paper. CBi and CM revised the manuscript and contributed to its improvement. PO coordinated the manuscript writing and contributed to the interpretation and discussion of this paper.All authors read and approved the final manuscript.

Funding source

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