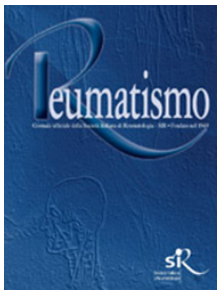

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Evaluation of tramadol/paracetamol 75 mg/650 mg combination therapy for early-stage knee osteoarthritis: a retrospective observational study

Alessandro Conforti,[1] Cosimo Ruggiero,[2] Nastasja Palombi,[3] Filippo Messina,[4] Marco Bonifacio,[5] Linda Lucchetti,[6] Marco Ruggiero,[7] Giuseppe La Cava,[8] Roberto Piazza,[3] Mario Mangrella[3]

[1]Local Health Rheumatology Unit, San Paolo Hospital, ASL Roma 4, Rome; [2]Pediatric Gastroenterology Unit, Policlinico Umberto I, Rome; [3]Medical Affairs Department, Italfarmaco SpA, Milan; [4]Radiology Unit, ASL Roma 4, Rome; [5]Civitavecchia, Rome; [6]Hospital Pharmacy Unit, ASL Roma 4, Rome; [7]IOR – Complex Structure of Orthopedics and Traumatology, Rizzoli-Argenta, Bologna; [8]Division of Orthopedic Surgery, San Paolo Hospital, Civitavecchia, Italy

Correspondence: Alessandro Conforti, Local Health Rheumatology Unit, San Paolo Hospital, ASL Roma 4, Via Largo Donatori del Sangue 1, Rome, Italy.
Tel.: +39 388 8162908.
E-mail: alessandro.conforti@aslroma4.it

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Contributions: AC, FM, MB, MR, study concept/design; AC, data acquisition; AC, CR, GLC, data analysis and/or interpretation; CR, statistical analysis; AC, NP, RP, MM, drafting the work or reviewing it critically for important intellectual content. All the authors approved the final version of the manuscript.

Conflict of interest: Nastasja Palombi, Roberto Piazza and Mario Mangrella are employed at Italfarmaco SpA. The other authors declare no potential conflict of interest.

Ethics approval and consent to participate: the study received approval from the Ethical Committee (protocol number C 0.1 RSO ID 2249) and was performed in accordance with the required regulatory specifications, in compliance with the Declaration of Helsinki and the ICH-Good Clinical Practice.

Informed consent: all study participants provided informed written consent.

Patient consent for publication: not applicable.

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Summary
Objective. Knee osteoarthritis (KOA) is a progressive joint disorder that significantly impairs patients' quality of life. Effective long-term management of KOA remains challenging due to limited pharmacological options and associated adverse effects. This monocentric, retrospective observational study evaluated the efficacy and safety of a fixed-dose tramadol/paracetamol combination (75/650 mg) in alleviating pain in patients with grade I-II KOA according to the Kellgren-Lawrence classification.
Methods. A total of 30 patients treated for 15 days were assessed using the Numerical Rating Scale for pain, the Western Ontario and McMaster Universities Osteoarthritis Index for functional impairment, and the Pittsburgh Sleep Quality Index for sleep quality.
Results. Results showed a 30% and 50% pain reduction in 86% and 43% of patients, respectively, alongside significant improvements in functional mobility and sleep quality. Adverse events, including nausea, itching, and sleepiness, occurred in 10% of patients and did not necessitate treatment discontinuation. Efficacy was consistent across demographic and clinical subgroups, possibly suggesting broad treatment applicability.
Conclusions. While the findings could support tramadol/paracetamol as a safe and effective first-line therapy for KOA, reinforcing its role in optimizing KOA management strategies, limitations such as the small sample size and lack of a control group highlight the need for further research.

Introduction

Osteoarthritis (OA) is a progressive joint disorder representing the primary cause of disability in adults (1). It is characterized by the gradual deterioration of articular cartilage, associated with remodeling and deformity of the articular surfaces in advanced stages (2-4). OA progression results in severe symptoms such as joint pain, stiffness, swelling, functional impairment, and joint noises like cracking or grinding during movement (5, 6), leading to impaired mobility, mood, and sleep, and ultimately diminishing patients' overall quality of life (QoL) (7). Additionally, OA often coexists with cardiovascular and metabolic diseases (8-10), thus being associated with an elevated risk of mortality (11).

OA affects an estimated 250 million people worldwide (1, 12), predominantly targeting major weight-bearing joints. Among its forms, knee osteoarthritis (KOA) is particularly prevalent and disabling (7, 13-15). Approximately 13% of women and 10% of men aged 60 and older experience symptomatic KOA, with prevalence rising to 40% in those over 70 (16, 17). These rates are projected to increase with longer life expectancy and the growing prevalence of obesity, two major risk factors for OA (1). Currently, OA has no cure, and its management remains a significant clinical challenge, particularly over the long term (18, 19). A multidisciplinary approach is required, with pharmacological treatments often necessary to alleviate pain, maintain mobility, and ensure a satisfactory QoL (20-24). Current first-line pharmacological options refer to oral or topical non-steroidal anti-inflammatory drugs (NSAIDs), opioids, and paracetamol (25, 26). Despite their effectiveness, prolonged NSAIDs are associated with risks of gastrointestinal, renal, and cardiovascular adverse effects, particularly in older adults or patients with comorbid conditions (27, 28). Similarly, single treatments with opioids and paracetamol at high doses can induce adverse effects such as addiction and hepatic toxicity or cardiovascular events, respectively (28, 29).

The combination of tramadol, the most commonly prescribed opioid for OA, with paracetamol is endorsed by the World Health Organization's pain ladder for pain management (1). This approach has emerged as a safe and effective strategy in alleviating OA-related pain (25, 30), utilizing the complementary opioid and non-opioid analgesic properties to reduce pain intensity while maintaining tolerability (30). The combination offers the advantage of lower individual doses of each drug, effectively mitigating the risk of side effects associated with either component (26, 30). For these reasons, tramadol/paracetamol is increasingly suggested as a preferred choice over NSAIDs, particularly for patients with contraindications to NSAID use or increased risk of adverse effects (26, 28).

Evidence from preclinical and clinical studies demonstrated the efficacy and safety of oral administration of fixed-dose tramadol/paracetamol for alleviating pain, but real-world evidence is still needed to robustly confirm the safety and performance of this approach in OA patients (18).

This study aims to contribute to filling this knowledge gap through the evaluation of real-world data on the efficacy and safety of tramadol/paracetamol therapy in the management of pain associated with KOA. Insights gained from this study will contribute to optimizing treatment strategies for improved pain control and QoL in this patient population.

Materials and Methods

Study design

This is a non-profit, monocentric, retrospective, observational clinical investigation conducted at the Local Health Rheumatology Unit of the San Paolo Hospital ASL Roma 4 (Rome, Italy). The study received approval from the Ethical Committee (protocol number C 0.1 RSO ID 2249) and was performed in accordance with the required regulatory specifications, in compliance with the Declaration of Helsinki and the ICH-Good Clinical Practice.

Patients

The study analyzed the clinical records of patients suffering from symptomatic KOA and treated between November 2023 and June 2024 for moderate to severe pain with oral tablets of tramadol/paracetamol (Italfarmaco S.p.A., Milan, Italy) combination at the fixed dose of 75/650 mg/day for 15 consecutive days and in accordance with the approved indications for the drug. The selected clinical records referred to patients classified as grade I-II according to the Kellgren-Lawrence (KL) scale based on X-Ray imaging assessment, with grade 0 signifying no presence of OA and grade IV indicating severe OA (31).

Baseline data included age, disease duration, sex, baseline medication use, and the presence of cardiometabolic multimorbidity, defined as the presence of two or more of the following conditions: hypertension, type II diabetes, and dyslipidemia, assessed through prior medical diagnoses. These characteristics provided a comprehensive profile of the study population, ensuring a detailed evaluation of treatment effects across a range of patient demographics and clinical backgrounds, including the co-occurrence of cardiometabolic multimorbidity.

Patients were eligible for inclusion in the analysis if they met all the following criteria: adults aged 18 years or older, diagnosed with moderate pain [Numerical Rating Scale (NRS)≥6], grade I-II KOA as assessed using the KL scale, and treated with a fixed-dose (75/650 mg) combination of tramadol/paracetamol between November 2023 and June 2024. Additional requirements for inclusion referred to the absence of hypersensitivity to tramadol and paracetamol, of a history of substance dependence, of epilepsy not controlled by the relevant treatment, of treatment with monoamine oxidase inhibitors in the two weeks following the discontinuation of their administration or active malignancies, and the ability to provide informed consent.

Objectives and outcome measures

The primary objective of this study was to evaluate the efficacy of the tramadol/paracetamol (75/650 mg) fixed combination in reducing pain intensity among the selected adult patients. Pain was assessed using the NRS, a widely utilized tool for quantifying patient-perceived pain intensity (32, 33). The NRS requires patients to rate their pain on a scale from 0 to 10, where 0 indicates no pain and 10 represents the worst imaginable pain. Pain intensity was measured at baseline (day 0) and after 15 days of continuous treatment (day 15). The primary endpoint was evaluated by comparing NRS scores at baseline and follow-up. Moreover, the number of patients showing a reduction of at least 50% in NRS pain scores was assessed.

The study included several secondary endpoints to comprehensively evaluate the effects of the therapy. Assessment of symptoms and functional disability was evaluated through the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (34, 35). This tool includes 24 items divided into three subscales: pain (5 items on intensity during specific activities), stiffness (2 items assessing intensity in different circumstances), and functionality (17 items evaluating difficulty performing daily activities). Responses were recorded according to a Likert scale ranging from 0 (no symptom) to 4 (severe intensity or difficulty). Pain response was also analyzed after stratification of the dataset according to patient sex, duration of the disease, intended as the time elapsed since KOA diagnosis and symptom onset, and presence of cardiometabolic multimorbidity. Sleep quality was another secondary outcome evaluated as an indirect measure of overall QoL and assessed using the Pittsburgh Sleep Quality Index (PSQI) (36, 37). The PSQI was administered at baseline (day 0) and after 15 days of treatment to track improvements. All potential side effects were documented to determine the safety profile of the treatment.

Statistical analyses

The sample size was defined before the beginning of the study based on the detection of potential differences between pre- and post-treatment in terms of pain response rate. In our cohort, the response rate was estimated to range between 75% and 90%, with a maximum expected difference of 50%

between pre- and post-treatment. The calculation was conducted considering a bilateral Wilcoxon signed-rank test with a 5% probability of type I statistical error to achieve a statistical power of 80%. A sample of 35 patients was estimated to be sufficient to reach the expected statistical power. If the sample size was not met, a post-hoc power analysis was performed to calculate the actual statistical power of the test for the primary endpoint.

Data were expressed as median values and interquartile ranges for continuous variables, while frequencies were used for categorical data as appropriate. Variations from baseline to follow-up of continuous variables were analyzed by means of Wilcoxon signed-rank tests. To reduce the possibility of a statistical error due to regression to the mean, analysis of the primary endpoint was repeated after exclusion of extreme values. Differences in demographic continuous and categorical variables between patients showing a reduction of at least 50% in NRS and the remainder were analyzed through Mann-Whitney tests for nonparametric distributions or chi-square tests, respectively. A multivariate logistic regression was performed as explorative analysis to investigate which of the demographic characteristics could be associated with the primary outcome. Odds ratios were calculated with 95% confidence intervals.

Statistical significance was considered with α at 5%. Analyses were performed using SPSS Statistics v. 27 (IBM Corp., Armonk, N.Y., USA).

Results

Patient characteristics

After screening, 30 patients were included in the analysis. Demographic characteristics of included patients and clinical assessment at baseline are reported in Table 1. Patients were equally distributed between males and females and had a median age of 64 (59-71) years. The median weight and height of the patients were 75 (67-84) kg and 168 (158-172) cm, respectively. Cardiometabolic comorbidities were present in 43% of the patients (13/30), while 47% (14/30) were smokers. Depression was reported in 30% of the patients (9/30). The median time since diagnosis was 60 (56-64) months, coinciding with the median time since symptom onset, with a median symptom duration of 3 (1-6) years.

Baseline scores indicated moderate pain, impaired functional mobility and sleep quality (Table 1), reflecting the burden of OA -related symptoms and their impact on patients' QoL.

Primary and secondary endpoints

The reduction in NRS from baseline [6 (5-7)] to follow-up [4 (2-5)] was significant ($p=0.03$), with a calculated post-hoc statistical power of 99%) (Figure 1). Overall, 86% of patients (26/30) showed a pain reduction of at least 30% and 43% (13/30) of patients achieved pain reduction of at least 50% at follow-up, with a significant decrease of NRS scores from baseline [6 (5-7)] to follow-up [2 (1-3)] ($p<0.001$, Figure 2). Analyses repeated after the exclusion of extreme values (min=2, max=9) confirmed a significant reduction in NRS scores in both the entire cohort ($p=0.038$) and the subgroup of patients achieving at least a 50% reduction ($p<0.001$).

Significant improvements were also observed in both WOMAC total score from baseline [49 (41-52)] to follow-up [36 (26-41)] ($p=0.03$) and the subscale scores for pain from baseline [10 (8-13)] to follow-up [7 (5-9)] ($p=0.02$), stiffness from baseline [5 (4-6)] to follow-up [2 (1-4)] ($p=0.04$) and physical function from baseline [28 (25-35)] to follow-up [22 (18-30)] ($p=0.04$) (Figure 3). Significant amelioration of sleep quality according to the PSQI was also observed from baseline [9 (7-14)] to follow-up [7 (5-9)] ($p<0.046$) (Figure 4).

There were no statistically significant differences in demographic or clinical variables (*e.g.*, age, sex, weight, disease duration, depression, or cardiometabolic profile) between patients showing pain reduction $\geq 50\%$ and the remaining ones ($p>0.05$) (Table 2).

The explorative multivariate logistic regression analysis including age, sex, weight, disease duration and cardiometabolic comorbidity as predictors found no significant result ($p>0.05$), as detailed in Table 2.

Safety

Adverse events occurred in 3 patients (10%) and consisted of nausea, itching and sleepiness. None of the patients experiencing adverse events required medical intervention or hospitalization. None of them suspended the treatment.

Discussion and Conclusions

Results from the present study indicate that oral administration of tramadol/paracetamol 75/650 mg is safe and effective for managing pain in patients with KOA staged as grade I-II according to the KL scale, possibly suggesting an improvement of the overall QoL.

Pain relief measured through NRS was meaningful, with 43% of patients achieving at least 50% reduction in pain intensity and almost 90% of patients achieving at least 30% pain reduction. These results are in line with previous studies reporting the administration of tramadol/paracetamol at comparable doses (38-41) and underscore the possible clinical benefit provided by the treatment, as 20% pain reduction already represents a clinically important difference (42). The effectiveness of the analgesic effect is even more notable considering the short treatment duration (15 days). Other trials corroborate early pain relief after tramadol/paracetamol combination, reporting pain reduction even after 5-10 days of treatment in patients experiencing OA flares (43). However, this is the first report highlighting that almost half of the treated patients had their pain intensity halve within 15 days. Altogether, these findings can support the utility of tramadol/paracetamol for short-term symptom management in KOA (and particularly at early stages), potentially offering a bridge to longer-term interventions such as physical therapy (44).

The improvements in functional disability and sleep quality observed from our analysis possibly suggest potential multifaceted benefits of the analgesic therapy combination. Similar results were reported in other studies showing improvements in WOMAC scores and sleep disturbance in KOA patients after administration of tramadol/paracetamol (38, 45). Although no universally accepted minimal clinically important difference threshold exists for the WOMAC scale, a reduction of 13 points in the total score, of 3 points for both pain and stiffness, and of 6 points for functional sub-score observed in this study could already suggest a clinically relevant benefit of the intervention (46-48). Functional impairment and sleep disturbances are primary drivers of reduced QoL in OA, creating a cycle of pain, inactivity, fatigue, low self-esteem, and even depression (49-54). Therefore, the fast analgesic effect of tramadol/paracetamol may prevent a clinical drift extending beyond the mere sphere of physical pain and disability (55). Although these results are only explorative in nature and need to be interpreted with caution, they contribute to widening clinical evidence on the benefits of the treatment, which can be explored in future trials.

Our study also suggests that tramadol/paracetamol treatment efficacy could be uniform across demographic and clinical subgroups, in line with results by other authors (45). Neither age, sex, weight, nor co-occurrence of cardiometabolic morbidities influenced the likelihood of achieving the primary outcome. This result could lend evidence to the broad applicability of the tramadol/paracetamol combination for diverse patient populations. However, these secondary endpoints should be considered as purely exploratory too and need to be interpreted with caution.

The pharmacological rationale for the efficacy observed in this study probably lies in the complementary mechanisms of tramadol and paracetamol. Tramadol acts as a weak opioid agonist, engaging μ-opioid receptors and modulating monoaminergic neurotransmission by inhibiting serotonin and norepinephrine reuptake (56). This dual action provides effective relief for both nociceptive and neuropathic components of pain (57, 58). Paracetamol, on the other hand, exerts its effects peripherally by inhibiting prostaglandin synthesis and centrally through serotonergic pathways

(59). The synergistic action of tramadol and paracetamol enables robust analgesia at lower doses of each drug, thereby minimizing the risk of dose-dependent side effects (30). The possibility of titration protocols further enhances tolerability, thereby improving compliance and the overall effect of the treatment (60, 61).

Dosage of 75/650 mg showed favorable safety outcomes, with mild adverse events reported in 10% of patients, none requiring treatment discontinuation, in line with a low incidence of adverse events due to tramadol/paracetamol administration (38). Importantly, no signs of opioid addiction were observed in the included patients, indicating that this side effect may primarily affect individuals with a predisposition.

Even though the favorable safety profile of tramadol/paracetamol combination could be superior to NSAID-based treatments or alternative opioid combinations (38), we underline the need to tailor treatment strategies to individual patient profiles and disease stages (62). Previous studies, for instance, demonstrated that tramadol/paracetamol could be preferred to NSAIDs, particularly in patients at risk of gastrointestinal, cardiovascular, or renal complications (43, 45). Our analysis may be useful to assess more comprehensively the safety profile of tramadol/paracetamol treatment in patients suitable for this approach.

The limitations of the study refer to the small sample size, the retrospective design, the lack of a control group, and the short follow-up period, which reduce the possibility of drawing definitive conclusions about the long-term efficacy and safety of the treatment. The absence of a control group prevents a direct demonstration of the treatment efficacy over changes that could instead be attributed to a placebo effect, a natural attenuation of symptoms, or a regression to the mean phenomenon over time. Moreover, it limits the possibility to compare treatment performance against standard therapies, such as NSAIDs or other opioid combinations, in the study population. A further limitation refers to the possible occurrence of multiplicity in the analysis of secondary endpoints, which could have increased the risk of type I error and led to misinterpretation. For this reason, secondary endpoints should be only considered explorative in nature, and results need to be interpreted with caution.

In conclusion, this study suggests that the fixed-dose tramadol/paracetamol combination could be an effective alternative in reducing pain, improving functional mobility, and enhancing sleep quality in patients with mild KOA. The favorable safety profile and consistent effectiveness across patient subgroups could support its value as a first-line pharmacological treatment. These findings, combined with the mechanistic rationale for the drug's efficacy, suggest that integrating the fixed-dose tramadol/paracetamol treatment into clinical practice could offer a practical and well-tolerated option for addressing the multifaceted challenges of KOA management.

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Table 1. Demographic characteristics of the included patients and anamnestic/clinical data at baseline. Continuous variables are summarized as median [interquartile range] and categorical variables as absolute and relative frequencies. Baseline scores for pain according to the Numeric Scale Rating, functional disability according to the Western Ontario and McMaster Universities Index, and sleep quality according to the Pittsburgh Sleep Quality Index are also reported. Co-occurrence of cardiometabolic disease was defined if at least two among hypertension, type II diabetes and dyslipidemia were diagnosed.

Characteristic (n=30)		Median [IQR] / n (%)
Age (years)		64 [59-71]
Sex	Male	15 (50)
	Female	15 (50)
Weight (kg)		75 [67-84]
Height (cm)		168 [158-172]
Cardiometabolic disease	Yes	13 (43.33)
	No	17 (56.67)
Smoking	Yes	14 (46.67)
	No	16 (53.33)
Depression	Yes	9 (30)
	No	21 (70)
Symptom duration (years)		3 (1-6)
Diagnosis (years)		60 [56-64]
Baseline NRS score		6 [5-7]
Baseline WOMAC score	Total	49 [41-52]
	Pain	10 [8-13]
	Stiffness	5 [4-6]
	Physical function	28 [25-34]
Baseline PSQI score		9 [7-14]

IQR, interquartile range; NRS, Numeric Scale Rating; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index: PSQI, Pittsburgh Sleep Quality Index.

Table 2. Output of the analyses performed to analyze differences in demographic and clinical data between patients showing a reduction of at least 50% and patients showing a reduction <50% in Numeric Scale Rating pain scores. Continuous variables are presented as median [IQR], and categorical variables as absolute and relative frequencies. Results of the multivariate logistic regression considering frequency of patients with pain reduction ≥50% or <50% as dependent variable are also shown indicating odds ratio and the 95% confidence interval.

Variable	Category	Pain reduction ≥50% (n=13)	Pain reduction <50% (n=17)	p-value
Age (years)		64 [53-78]	64 [60-70]	0.93[a]
Weight (kg)		73 [70-90]	78 [67-80]	0.46[a]
Disease duration (years)		4 [2-6]	3 [1-6]	0.61[a]
Disease duration categories	*<5y*	8 (26.7%)	11 (36.7%)	1.00[b]
	>5y	5 (16.7%)	6 (20%)	
Cardiometabolic disease	*Yes*	8 (26.7%)	7 (23.3%)	0.46[b]
	No	5 (16.7%)	10 (33.3%)	
Depression	*Yes*	3 (10%)	6 (20%)	0.75[b]
	No	10 (33.3%)	11 (36.7%)	
		OR [95% CI]		
Sex	Male (ref.)	–		–
	Female	0.40 [0.08-1.91]		0.25[d]
Cardiometabolic disease	No (ref.)	–		–
	Yes	0.48 [0.09-2.69]		0.40[d]
Age (years)[c]		1.02 [0.92-1.13]		0.74[d]
Weight (kg)[c]		1.02 [0.95-1.10]		0.52[d]
Disease duration (years)[c]		1.00 [0.99-1.00]		0.44[d]

[a]Mann-Whitney test; [b]Chi-square test; [c]for every one-unit increase; [d]multivariate logistic regression; OR, odds ratio; CI, confidence interval.

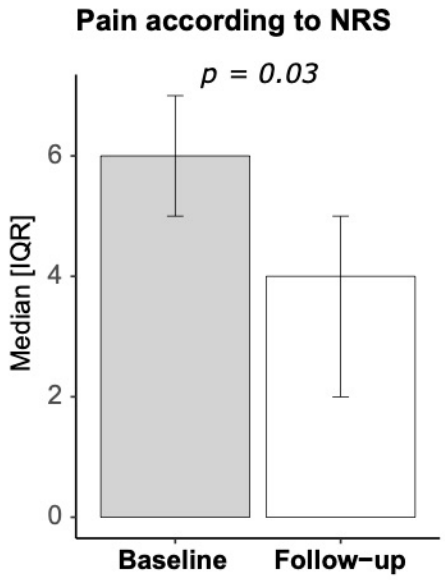

Figure 1. Outcome of pain according to the Numeric Rating Scale (NRS) at baseline and 15-day follow-up. Data are reported as median and interquartile range (IQR=. The p-value (p) of the test is shown above the bars.

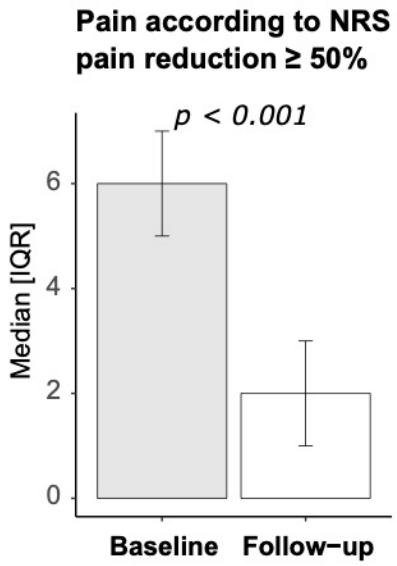

Figure 2. Outcome of pain according to the Numeric Rating Scale (NRS) at baseline and 15-day follow-up in patients showing at least 50% pain reduction. Data are reported as median and interquartile range (IQR). The p-value (p) of the test is shown above the bars.

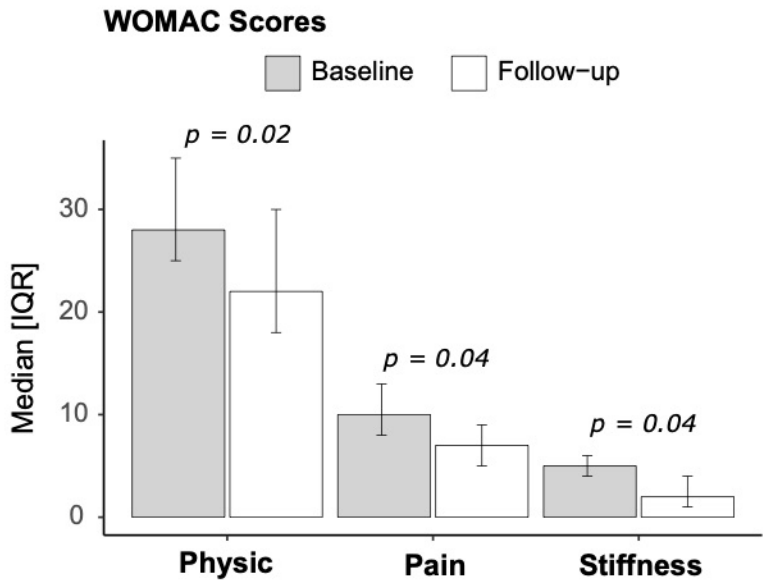

Figure 3. Outcomes of the WOMAC Score for pain, stiffness, and physical functionality at baseline and 15-day follow-up. Data are reported as median and interquartile range (IQR). The p-value (p) of the test conducted on each sub-score is shown above the bars.

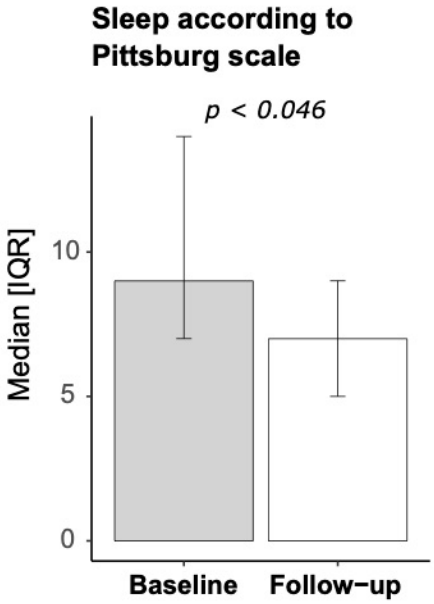

Figure 4. Outcome of sleep quality according to the Pittsburgh questionnaire at baseline and 15-day follow-up. Data are reported as median and interquartile range (IQR). The p-value (p) of the test is shown above the bars.