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Efficacy of ultramicronised diclofenac in patients with osteoarthritis – systematic review with network meta-analysis

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Abstract. – OBJECTIVE: This systematic review with network meta-analysis was performed to compare the effectiveness of oral anti-inflammatory drugs used in Brazil for osteoarthritis.

PATIENTS AND METHODS: Randomized clinical trials evaluating ultramicronised diclofenac, diclofenac, celecoxib, etodolac and placebo in patients with osteoarthritis were identified. A search was conducted in May 2021 through PubMed, Scopus and Web of Science databases. A network meta-analysis was developed for efficacy outcome related to analgesia measured by the pain subscale of the Western Ontario and McMaster Universities tool. In addition, surface under the cumulative ranking was performed to rank the drugs in relation to this outcome.

RESULTS: Twelve randomized clinical trials were included. Overall, ultramicronised diclofenac 105 mg/day (UD105) was better than all the others, including ultramicronised diclofenac 70 mg/day (UD70). In addition, surface under the cumulative ranking resulted in the following order: 1) ultramicronised diclofenac 105 mg/day (100%), 2) ultramicronised diclofenac 70 mg/day (80%), 3) celecoxib 200 mg/day (49%), 4) diclofenac 100 mg/day (48%), 5) placebo (19%) and 6) diclofenac 150 mg/day (6%).

CONCLUSIONS: Ultramicronised diclofenac demonstrated superior efficacy compared to other conventional anti-inflammatory drugs and placebo in relieving osteoarthritis pain.

Key Words:
Diclofenac, Celecoxib, Network meta-analysis, Osteoarthritis, Pain, Anti-inflammatory agents.

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most prescribed pharmacological classes in the world, being widely used to treat a variety of pain conditions, especially in the context of osteoarticular diseases[1]. Osteoarthritis (OA) is the most frequent joint disease in the world population, with prevalence of 10-15% in people aged over 60 years, with NSAIDs as one of the main therapeutic classes used in pain management related to this condition[2-4].

Despite their widespread use, NSAIDs are associated with a risk of gastrointestinal, hepatic, cardiovascular and renal adverse events, some of which are potentially serious, such as gastrointestinal bleeding, acute myocardial infarction, and acute renal failure[1,2,5,6]. The risk of occurrence of such adverse events presents a dose-dependent behaviour, with higher doses and longer treatment duration being related to greater toxicity. Thus, regulatory agencies such as the Food and Drug Administration (FDA) recommend NSAIDs to be used 'at the lowest effective dose, for the shortest possible duration necessary to achieve the treatment goals', in attempt to minimise the risk of complications[7]. On the other hand, simply reducing the dose of NSAIDs, although capable of increasing safety, may imply a lower analgesic and anti-inflammatory effect, potentially compromising effectiveness[8].

Ultramicronised diclofenac is a new nanoformulation of diclofenac, in which the drug particles are subjected to an ultramicronisation process, resulting in a final size 10-20 times smaller than conventional diclofenac particles. The considerable reduction in the average size of the particles allows for better dissolution of the drug and, consequently, greater absorption in the gastrointestinal tract, allowing the use of a lower dose without compromising therapeutic efficacy[8].

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Table I. Search strategy.

Databases	Search strategy
Pubmed 10.983	(((((((((diclofenac[Title/Abstract]) OR((solumatrix[Title/Abstract] AND diclofenac[Title/Abstract])) OR (bexai[Title/Abstract])) OR (celecoxib[Title/Abstract])) OR (celebra[Title/Abstract])) OR (etodolac[Title/Abstract]))) OR (diclofenac[MeSH Terms])) OR (Flancox[Title/Abstract])) AND Search ((((((clinical[Title/Abstract]) AND trial[Title/Abstract]) OR 'clinical trials as topic'[MeSH Terms]) OR 'clinical trial'[Publication Type]) OR random*[Title/Abstract]) OR 'random allocation'[MeSH Terms]) OR 'therapeutic use'[MeSH Subheading]
Scopus 1.973	(TITLE-ABS(diclofenac OR (solumatrix AND diclofenac) OR bexai OR celecoxib OR celebra OR etodolac OR Flancox)) AND (TITLE-ABS((random AND trial) OR (clinical AND trial) OR 'clinical study'))
Web of science 2.412	((TÓPICO: ((((((diclofenac OR (solumatrix AND diclofenac)) OR bexai) OR celecoxib) OR celebra) OR etodolac) OR Flancox)) AND TÓPICO: (((random AND trial) OR (clinical AND trial)) OR 'clinical study'))

Note: Searches were conducted in May 2021.

The aim of this study was to comparatively evaluate, through a systematic literature review and network meta-analysis, the analgesic efficacy of ultramicronised diclofenac, sodium/potassium diclofenac, etodolac and celecoxib in the treatment of patients with OA.

Patients and Methods

All steps of this systematic review (SR) were conducted based on the guidelines of the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA)[9,10] and recommendations of the *Cochrane Collaboration*[11].

Search Strategy and Eligibility

In order to compare the anti-inflammatory drugs: ultramicronised diclofenac, diclofenac, etodolac and celecoxib at different dosages commercially approved in Brazil, a search was performed in May 2021through PubMed, Scopus and Web of Science databases. The search strategy for each database is presented in Table I. In addition, a manual search was performed through the reference list of the included studies and through grey-literature search.

After removing duplicates, two independent reviewers screened articles by evaluating titles and abstracts, and then read the selected articles in full. In cases of discrepancy, a third reviewer was also consulted. Randomised clinical trials (RCTs) that evaluated the effectiveness (analgesia) by the Western Ontario and McMaster Universities (WOMAC) pain subscale of at least two of the proposed oral drugs (ultramicronised diclofenac, celecoxib, diclofenac, etodolac and placebo) at commercially available doses in Brazil in adult patients with OA (>18 years) requiring analgesic treatment were included in the SR.

Only studies in English, Portuguese and Spanish were included. Studies that addressed drug combination, subanalyses of other studies or post hoc analyses were excluded.

Data Extraction

Data extraction was performed using Excel software, extracting the following information from the included studies: study data (authors, year of publication and study center), baseline characteristics of the population (age, sample size) and outcome results of analgesia measured by the pain domain of the *Western Ontario and McMaster Universities* (WOMAC) instrument.

Statistical Analysis

For the comparison of interventions, a network meta-analysis (NMA) was performed, as this allows for the simultaneous direct and indirect comparison of medications. This statistical analysis is based on Bayesian methods, in which the Markov chain Monte Carlo simulation method (MCMC) is used to generate combined effect sizes[12-15].

The results were expressed as mean difference (MD) in relation to the baseline and their respective 95% credible interval (CrI). Our final model adopted a random effect, as it is a more conservative analysis to explain the study variance. When necessary, subgroup and sensitivity analysis was performed considering the indications. To assess

whether there was a discrepancy between direct and indirect comparisons and to assess the strength of the network, an inconsistency and node split analysis was conducted[16-18].

In addition, surface under the cumulative ranking (SUCRA) was performed to rank the probability that one drug was better than the other for the analgesia outcome. SUCRA values range from 0 to 100%. The higher the SUCRA value, and the closer to 100%, the higher the likelihood that a therapy is in the top rank or one of the top ranks; the closer to 0 the SUCRA value, the more likely a therapy is in the lower rank[19]. Analyses were conducted using the ADDIS software version 1.17.6 (Aggregate Data Drug Information System; https://drugis.org/software/addis)[20].

Bias Risk Assessment

To measure the risk of bias, the Cochrane tool (RoB 2.0) was used[21]. The following domains were evaluated: bias due to the randomization process, bias due to deviation from intended interventions, bias due to lack of outcome data, bias in outcome measurement and bias in the selection of reported outcomes. The risk of bias was judged in each domain as 'low risk', 'high risk' or with 'some concerns', being assessed by two independent reviewers; in cases of discrepancy a third reviewer was consulted.

Results

After excluding duplicates, 14,427 studies remained for the screening process. Then 14,248 studies were excluded, with 179 studies to be read in full. Of these, 12 RCTs[22,23,32,24-31] (n = 4,767 patients) were included for data extraction. The characteristics of the included studies are shown in Table II and the number of studies included in each step of this SR is shown in Figure 1.

As mentioned, the dosages of the medications evaluated are only those available in Brazil, and the nomenclature given to each comparator refers to the total daily quantity of medications. Thus, the following dosages were identified: celecoxib 200 mg (C200), diclofenac 150 mg (D150) and 100 mg (D100), and ultramicronised diclofenac 105 mg (UD105) and 70 mg (UD70). No studies that met the established inclusion criteria were found to report the use of etodolac in patients with osteoarthritis.

The summary of the risk of bias assessment is presented in Table III. All studies had low overall risk of bias. Only a few studies showed 'some concerns' in the domain 'randomisation process' due to the lack of information about the randomisation process.

The NMA built for the outcome of analgesia efficacy measured by the pain subscale of the WOMAC tool is shown in Figure 2.

The NMA identified UD105 as superior to UD70 (MD 5.46; CrI 3.55-7.36), placebo (MD 12.45; CrI 10.62-14.38), D150 (MD 13.50; CrI 10.42-16.57), D100 (MD 10.78; CrI 7.47-14.13) and C200 (MD 11.05; CrI 8.91-13.05; Figure 3).

UD70 was statistically superior to C200 (MD 5.60; CrI 3.48-7.62), D100 (MD 5.35; CrI 1.93-8.71), D150 (MD 8.03; CrI 4.96-11.11) and placebo (MD 7.01; CrI 5.16-8.86; Figure 4).

Placebo proved to be less effective than C200 (MD –1.42; CrI –2.37 to –0.57; Figure 5), whereas

Table II. Main characteristics of the studies included in the systematic review.

Study	N	Treatment	Study design	Countries
Conaghan, 2013[22]	463	C200, Placebo	RCT, double blind	Czech Republic, Germany, Poland and the UK
Essex, 2014[24]	189	C200, Placebo	RCT, double blind	USA
Essex, 2016[23]	223	C200, Placebo	RCT, double blind	USA
Fleischmann, 2005[33]	678	C200, Placebo	RCT, double blind	Multicentric
Gibofsky, 2003[26]	378	C200, Placebo	RCT, double blind, Phase 3	Multicentric (USA and Canada)
Gibofsky, 2014[25]	304	UD 105, UD70, Placebo	RCT, double blind	Multicentric
Lee, 2017[27]	216	C200, Placebo	RCT, double blind	South Korea
Lehmann, 2005[28]	844	C200, Placebo	RCT, double blind	Multicentric
McKenna, 2001[29]	600	C200, D150, Placebo	RCT, double blind	USA
Rother, 2007[30]	259	C200, Placebo	RCT, double blind	Germany
Simon, 2009[31]	308	D100, Placebo	RCT, double blind	USA and Canada
Strand, 2017[32]	305	UD105, UD70, Placebo	RCT, double blind, Phase 3	USA

Abbreviations: C200, celecoxib 200 mg; D150, diclofenac 150 mg; D100, diclofenac 100 mg; UD105, ultramicronised diclofenac 105 mg; UD70, ultramicronised diclofenac 70 mg.

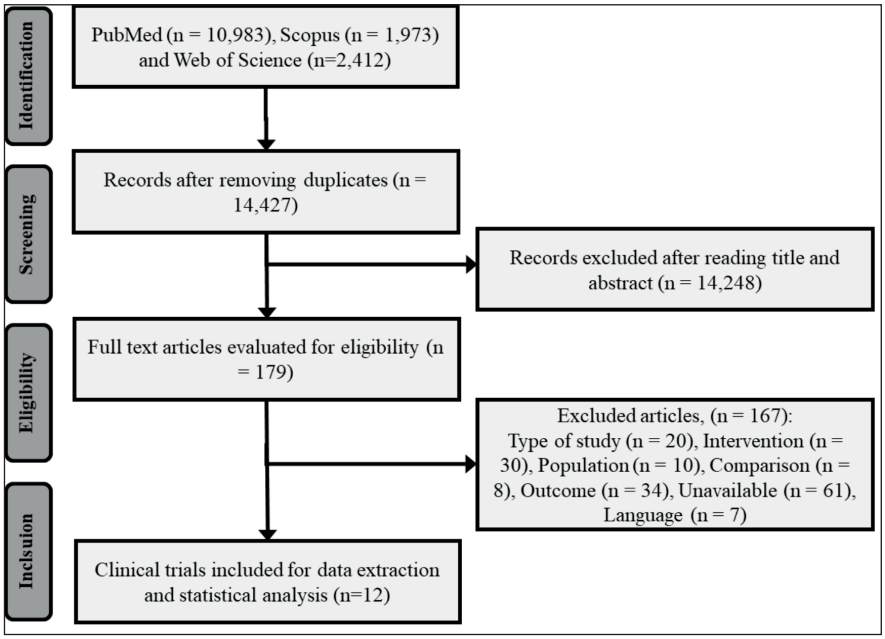

Figure 1. Systematic review flowchart.

C200 was superior to D150 (MD 2.45; CrI 0.07-4.95). There was no statistical difference in the comparison between D100 and D150, (MD 2.73; CrI –1.06–6.36).

The SUCRA resulted in the following ranking: 1) UD105 (100%), 2) UD70 (80%), 3) C200 (49%), 4) D100 (48%), 5) Placebo (19%) and 6) D150 (6%; Table IV).

Sensitivity analyses were conducted for the study outcome, considering the different regimens and methodological quality. However, no additional differences were found in the original analyses (data not shown). The network was considered robust for the evaluated result. No substantial differences ($p > 0.05$) were identified through the inconsistency analysis. The node split analysis was not performed due to the lack of direct and indirect comparisons of two drugs.

Table IV. SUCRA classification.

Rank	Treatment	SUCRA
1	UD105	100%
2	UD70	80%
3	C200	49%
4	D100	48%
5	Placebo	19%
6	D150	6%

Abbreviations: SUCRA, surface under the cumulative ranking; C200, celecoxib 200 mg; D150, diclofenac 150 mg; D100, diclofenac 100 mg; UD105, ultramicronised diclofenac 105 mg; UD70, ultramicronised diclofenac 70 mg; P, placebo.

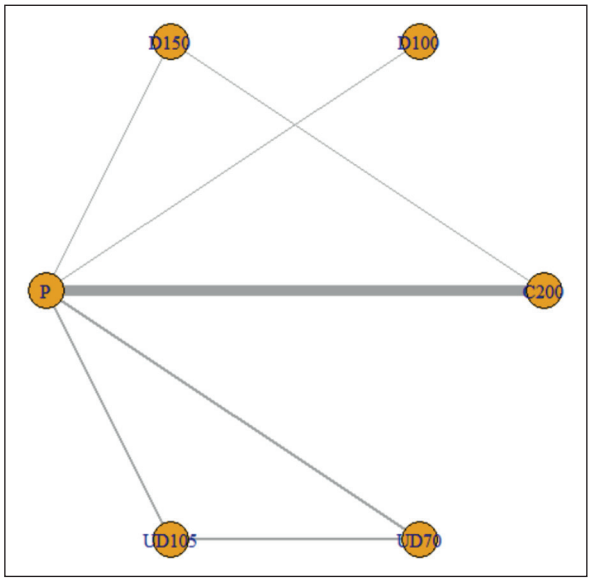

Figure 2. Network meta-analysis for analgesia outcome.Abbreviations: C200, celecoxib 200 mg; D150, diclofenac 150 mg; D100, diclofenac 100 mg; UD105, ultramicronised diclofenac 105 mg; UD70, ultramicronised diclofenac 70 mg; P, placebo

Discussion

In this NMA comparing the analgesic efficacy of different anti-inflammatory drugs in patients

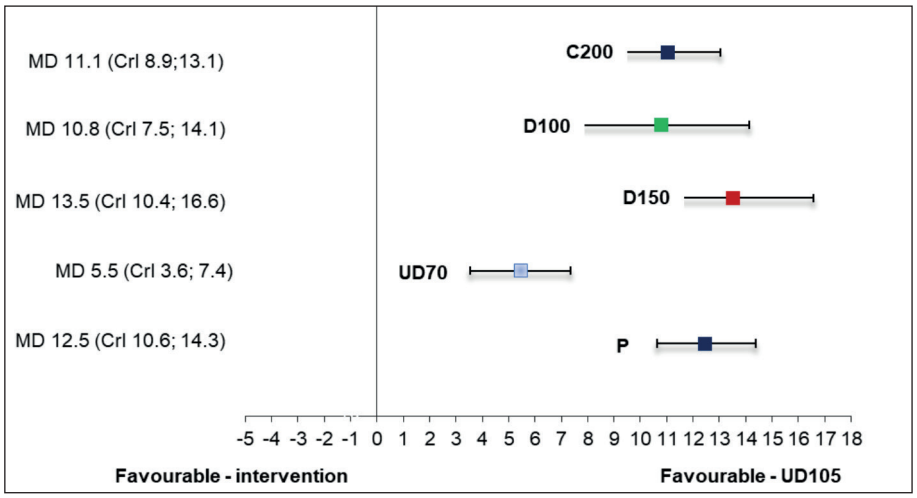

Figure 3. Forest plot comparing UD105 with other treatments.Abbreviations: MD, mean difference; C200, celecoxib 200 mg; D150, diclofenac 150 mg; D100, diclofenac 100 mg; UD105, ultramicronised diclofenac 105 mg; UD70, ultramicronised diclofenac 70 mg; P, placebo; CrI, credible interval.

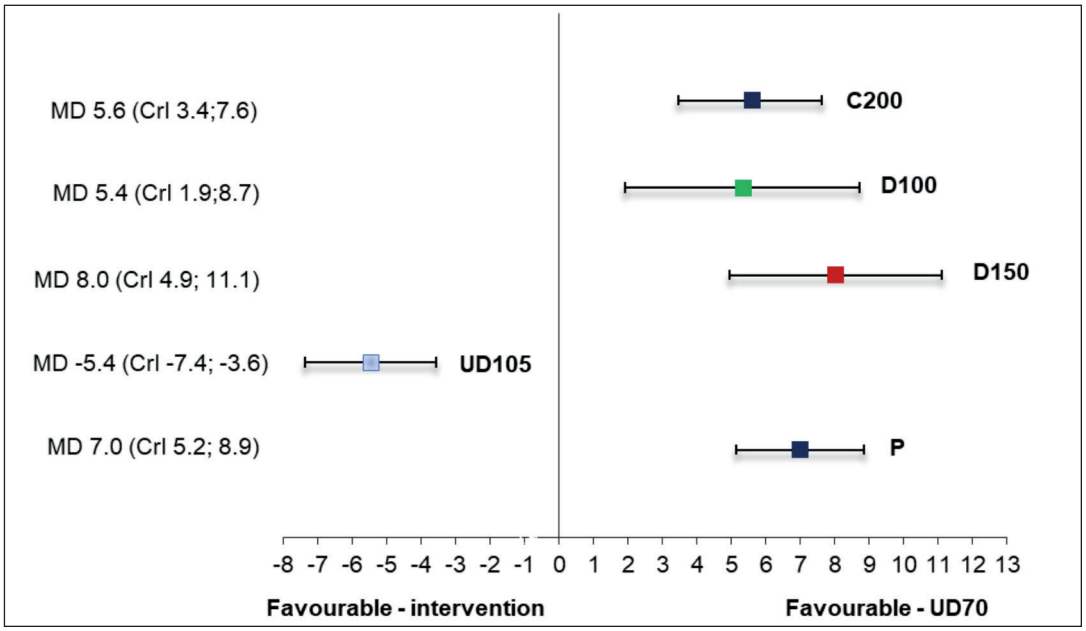

Figure 4. Forest plot comparing UD70 with other treatments. **Abbreviations:** MD, mean difference; C200, 200 mg celecoxib; D100, 100 mg diclofenac; D150, 150 mg diclofenac; UD70, 70 mg ultramicronised diclofenac; UD105, 105 mg ultramicronised diclofenac; P, placebo; CrI, credible interval

with OA, ultramicronised diclofenac proved to be the treatment option showing best results, both in comparison to placebo and to other active treatments. Ultramicronised diclofenac in 35 mg presentation taken three times a day (UD105) or twice daily (UD70) showed better analgesia results compared to diclofenac and celecoxib. To the best of our knowledge, this is the first study to compare ultramicronised diclofenac to other active treatments in patients with OA, showing that low doses of ultramicronised diclofenac are more effective in analgesia.

Two Phase 3 clinical trials evaluating ultramicronised diclofenac were identified in the SR. Gibofsky et al[25] evaluated the efficacy of UD105 and UD70 for 12 weeks compared to placebo in controlling pain in patients with OA. In this study, 35 mg ultramicronised diclofenac administered twice or three

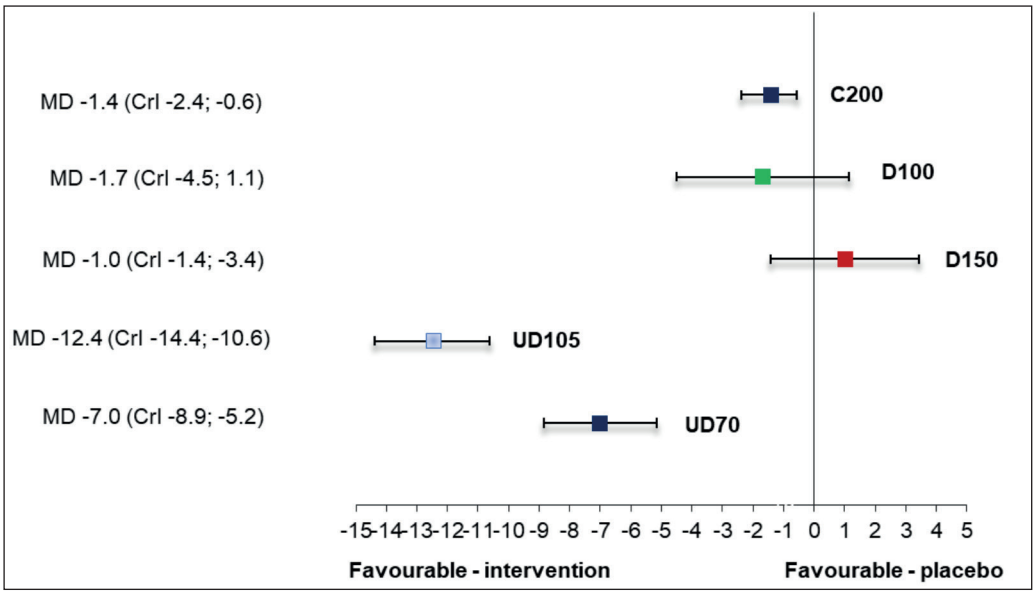

Figure 5. Forest plot comparing placebo with other treatments. Abbreviations: MD, mean difference; C200, 200 mg celecoxib; D100, 100 mg diclofenac; D150, 150 mg diclofenac; UD70, 70 mg ultramicronised diclofenac; UD105, 105 mg ultramicronised diclofenac; P, placebo; CrI, credible interval.

times a day resulted in a statistically significant studies differs from other published works such as the meta-analysis by Costa et al (2017)[33].

Besides the efficacy data, the study by Gibofsky et al (2014)[25] evaluated the safety profile of ultramicronised diclofenac, noting that none of the patients had ulcers, gastrointestinal bleeding or perforation, myocardial infarction, stroke or renal failure, and a small number of patients had to discontinue the treatment. Furthermore, an open study was conducted to analyze the use of ultramicronised diclofenac in 601 patients with OA for a period of up to 52 weeks. This study demonstrated that treatment was well tolerated and associated with improved quality-of-life measures, with only 16.5% of patients discontinuing treatment. Serious gastrointestinal, cardiovascular, renal and hepatic adverse events were uncommon[34].

The impossibility of performing a safety analysis of ultramicronised diclofenac in comparison to other active treatments was the main limitation of this meta-analysis. This was because only a few of the adverse events reported in the ultramicronised diclofenac studies were reported for other treatments, preventing the formation of an NMA for specific adverse events. Nevertheless, safety is probably one of the great advantages of ultramicronised diclofenac when compared to traditional diclofenac or other NSAIDs with conventional formulation. This is related to particle size reduction and consequent increase in surface area promotes increased bioavailability, making it possible to achieve analgesia with lower doses, decrease systemic exposure[35] and thus minimize the frequency and severity of adverse events while maintaining efficacy. Considering that patients with OA make chronic use of NSAIDs, further studies analysing the long-term effects of ultramicronised diclofenac would be of great interest. New safety and efficacy studies making direct comparisons between ultramicronised diclofenac and conventional NSAIDs are needed to assess this potential.

Conclusions

In this analysis, patients with osteoarthritis had greater pain relief through the use of ultramicronised diclofenac when compared to those who used conventional anti-inflammatory drugs or placebo.

Conflict of Interest

All authors work or received fees from a company, however this did not compromise the analysis.

Disclosure

GCC received a fee from NC Group as consulting fee. EAM was a full-time employee of NC Group during the development of this manuscript. LLA and AMK are full-time employees of NC Group. MPR and MMF are employees of a consultancy company hired by NC Group.

Author Declarations of Individual Contributions

GCC contributed to study concept, study design, data collection, data interpretation and writing of the manuscript. EAM contributed to study concept, study design, data interpretation and writing of the manuscript. AMK contributed to study design, data interpretation and writing and reviewing of the manuscript. MPR contributed to data collection, data analysis, data interpretation and writing of the manuscript MMF contributed to data collection, data analysis, data interpretation and writing of the manuscript. LLA contributed to study concept, study design and reviewing of the manuscript.

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