Efficacy of ketoprofen *vs.* ibuprofen and diclofenac: a systematic review of the literature and meta-analysis

P. Sarzi-Puttini[1], F. Atzeni[1], L. Lanata[2], M. Bagnasco[2]

[1]Rheumatology Unit, L. Sacco University Hospital, Milan, Italy;
[2]Medical Department, Dompé SpA, Milan, Italy.

Abstract

Objective
The aim of this systematic review of the literature and meta-analysis of randomised controlled trials (RCTs) was to compare the efficacy of orally administered ketoprofen with that of ibuprofen and/or diclofenac.

Methods
The literature was systematically reviewed in accordance with the Cochrane Collaboration guidelines. The search was restricted to randomised clinical trials published in the Medline and Embase databases up to June 2011, and comparing the efficacy of oral ketoprofen (50–200 mg/day) with ibuprofen (600-1800 mg/day) or diclofenac (75–150 mg/day).

Results
A total of 13 RCTs involving 898 patients met the inclusion criteria: eight comparing ketoprofen with ibuprofen, and five comparing ketoprofen with diclofenac. The results of the meta-analysis showed a statistically significant difference in efficacy in favour of ketoprofen. The difference between ketoprofen and the pooled ibuprofen/diclofenac data was also statistically significant (0.459, 95% CI 0.33-0.58; p=0.00) at all point-estimates of the mean weighted size effect. Ketoprofen was significantly superior to both diclofenac (mean = 0.422; 95% CI 0.19-0.65; p=0.0007) and ibuprofen (mean = 0.475; 95% CI 0.32-0.62; p=0.0000) at all point-estimates. Heterogeneity for the analysed efficacy outcome was not statisically significant in any of the meta-analyses.

Conclusion
The efficacy of orally administered ketoprofen in relieving moderate-severe pain and improving functional status and general condition was significantly better than that of ibuprofen and/or diclofenac.

Key words
ketoprofen, diclofenac, ibuprofen, efficacy

Piercarlo Sarzi-Puttini, MD,
Fabiola Atzeni, MD, PhD,
Luigi Lanata, MD,
Michela Bagnasco, PhD

Please address correspondence to: Pier-carlo Sarzi-Puttini, MD,
Dipartimento di Reumatologia,
Ospedale Universitario L. Sacco,
Via G.B. Grassi 74,
20127 Milano, Italy.
E-mail: sarzi@tiscali.it

Introduction

The management of mild-to-moderate pain has traditionally been based on the use of non-steroidal anti-inflammatory drugs (NSAIDs) and the synthetic non-opioid analgesic paracetamol (acetaminophen), both of which are effective, widely recommended, and extensively used (1). Among the NSAIDs, ketoprofen, ibuprofen and diclofenac have been used for the last 30 years (1-3). Ketoprofen is potent and effective in relieving pain due to traumatic, orthopedic and rheumatic disorders because of its anti-inflammatory and analgesic properties (1). Its main mechanism of analgesic action is the inhibition of cyclo-oxygenase (COX), which decreases the production of prostaglandin E2 (PGE2), but it also inhibits the lipoxygenase pathway of the arachidonic acid cascade (4), thus decreasing leukotriene synthesis. Furthermore, like other NSAIDs, it has both peripheral and central sites of activity (5) as a result of inhibiting central prostaglandin biosynthesis (6, 7) by inhibiting brain COX and nitric oxide synthase. It has been shown that the analgesic efficacy of its oral administration to patients with chronic rheumatic diseases such as osteoarthritis (OA) and rheumatoid arthritis (RA) is greater than that of naproxen or acetylisalicylic acid. A comparative multicentre study evaluating the efficacy and tolerability of ketoprofen and diclofenac sodium in subjects with acute rheumatic and traumatic conditions showed an improvement in pain symptoms, with complete pain relief being observed in 25% of the patients treated with ketoprofen as against 10% of those treated with diclofenac (8). An interesting multicentre, double-blind study of 165 patients with traumatic pain-related sports injuries compared the analgesic efficacy of one week's treatment with ketoprofen (50 mg/b.i.d. per os) or ibuprofen (600 mg/b.i.d per os), and found that 50% pain relief was achieved by more of the patients treated with ketoprofen (76% *vs*. 58%; *p*<0.05) and in a shorter time (9).

In our meta-analysis we decided to include only trials comparing directly ketoprofen with ibuprofen and/or diclofenac; this approach was actually followed to guarantee the homogeneity between studies and to lower the risk of bias.

The aim of this systematic literature review and meta-analysis of RCTs was to compare the pain relieving efficacy of ketoprofen with that of ibuprofen and diclofenac.

Methods

The meta-analysis was designed and performed in accordance to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement (10).

Literature search

A systematic search was made of the Medline and Embase electronic databases up to June 2011 in order to identify clinical trials comparing ketoprofen with ibuprofen or diclofenac following a previously defined protocol. No geographical neither language limits were applied. The search was extended to grey literature sources, such as abstract from Annual Scientific Meetings of the American College od Rheumatology (ACR) congress, European League Against Rheumatism (EULAR) congress from 2009 to 2011, non peer review or unpublished randomised trials. The databases were searched using various combinations of the key words: "clinical trial", "ibuprofen", "Brufen", "diclofenac" "Voltaren", "Orudis", "OKi" and "ketoprofen".

We applied inclusion and exclusion criteria by subquestions and designs. All PRISMA steps were followed, including checklist (data not shown).

Study selection

All selected titles and abstracts were independently reviewed by two rheumatologists (PCSP and FA) in accordance with the Cochrane Collaboration guidelines (11).

The inclusion criteria used to select the studies were established *a priori* and included prospective RCTs involving patients aged >18 years that compared the clinical efficacy of oral ketoprofen in treating moderate-severe pain with that of oral ibuprofen or diclofenac, with or without a placebo control group.

Furthermore, in order to guarantee the

adherence to therapeutic doses and the homogeneity of the effect sizes, we only included trials in which ketoprofen, ibuprofen and diclofenac were used at daily doses within the respective therapeutical ranges of 50-200 mg/day, 600-1800 mg/day, and 75-150 mg/day. These doses are in accordance with the posology recommended in clinical practice for the treatment of moderate to severe pain.

The clinical trials that did not concentrate on efficacy were excluded, as were those that did not directly compare ketoprofen with diclofenac or ibuprofen, those which compared ketoprofen with diclofenac or ibuprofen combined with a narcotic or non-narcotic agent, those in which the NSAIDs were not administered orally or administred at daily doses outside the specified therapeutical ranges. Retrospective studies were excluded to minimise heterogeneity, and no consideration was given to reviews, letters, editorials, conference papers, case reports, basic science papers or clinical practice guidelines.

Initially, the titles and/or abstracts of all of the identified trials were reviewed independently by two of the authors. This was followed by a second review of the eligible full-text publications using a recognised method of positive inclusion. Disagreements regarding the inclusion of articles were resolved by discussions involving all of the authors.

Study quality assessment and risk of bias in included studies
The quality of the selected publications was assessed using Jadad's RCT assessment scale (12), which assesses blinding, randomisation and dropouts/withdrawn patients. The scale scores range from 0 to 5, with higher scores indicating less likelihood of bias in the results and a score of ≥3 indicating high quality. However, we also assessed articles with a Jadad score of <3 because of the limited number of studies comparing ketoprofen with the other two NSAIDs.

Moreover, using the guidelines in the Cochrane Handbook for assessment of risk of bias (RoB), the clinical trials were graded by two reviewers (PCSP and FA) basing on sequence genera-
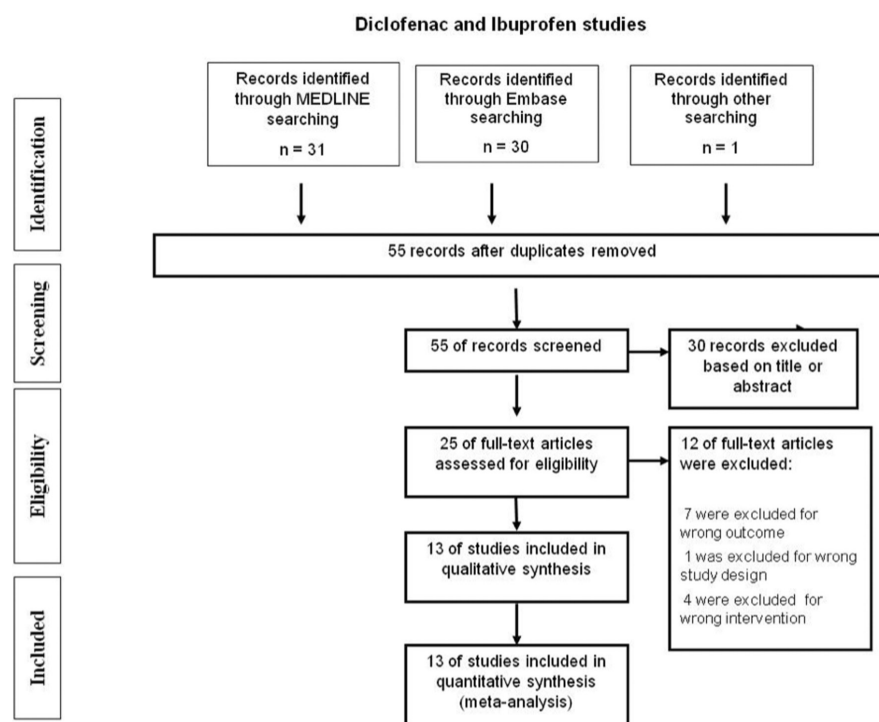

Fig. 1. Flow chart of the selection process.

tion, allocation concealment, incomplete outcome data, selective outcome reporting, blinding of participants and personnel and blinding of outcome assessment (11). These items were considered as key domains for RoB assessment and classified as "adequate" (low risk of bias), "inadequate" (high risk of bias), or "unclear". Studies with adequate procedures in all domains were considered to have a low risk of bias; ones with inadequate procedures in one or more key domain(s) were considered to have a high risk of bias; and ones with unclear procedures in one or more key domain(s) were considered to have an unclear risk of bias.

Data extraction and outcome definition
The data were extracted using a predefined data extraction form. The extracted information included first author, the year of publication, the study design, its Jadad quality score, the type of disease, the number of patients and controls, the type of NSAIDs and their doses, treatment duration, mean age/gender ratios, and outcome measure(s). The parameters and scores collected from all of the articles were pain (visual analogue scale [VAS]), pain (0–4 point scale), pain (0-20 point scale), pain (1-5 point scale), pain relief (0–4 point scale), responders (pain relief score >2: *i.e.* 50% pain relief), total symptom rating score (0–4 point scale), joint index, and the percentage of improved patients *vs.* the percentage of unimproved patients.

Statistical analysis
The meta-analysis was made using the standardised mean differences (SMD) of each RCT. The weighted mean difference and the 95% confidence interval (95% CI) were obtained by the combining standardised mean differences using a fixed effects model. The statistical heterogeneity of the standardised mean differences was assessed using Cochrane's Q statistic, which shows the variation across studies due to heterogeneity and can be used to assess the consistency of the evidence (13-15). I^2 statistic was also calculated, which measures the percentage of total variation across trials. Here, values between 0% and 40% can be interpreted as unimportant heterogeneity, up to 60% as moderate heterogeneity and over 60% as considerable heterogeneity (11, 16, 31). We assessed publication bias graphically, using funnel plots of standard

Table I. Characteristics of the RCTs comparing ketoprofen *vs*. ibuprofen.

Author, year	Study design	Jadad score	Treatment group dose/day	Treatment duration	Type disease	No. of patients	Sex M/F	Outcome measures used for meta-analysis
Calin, 1977	Randomised double blind, parallel group	4	K (150-300 mg) I (1200-2400 mg)	3 months	RA	52 50	23/29 22/28	Joint index
Giaccai, 1978	Randomised double blind, parallel group	1	K (160 mg) I (1200 mg)	3-15 days	OA	12 12	8/16	Clinical judgement of patients improved
Huskisson 1976	Randomised double blind, crossover	4	K (150 mg) I (1200 mg) F (2400 mg) N (500 mg)	2 weeks	RA	90 90 90 90	nd	Pain intensity (0–20 point scale)
Mehlisch 1988	Randomised double blind, crossover	5	K (150 mg§) I (800 mg§)	3 days	Dysmen.	37 37	0/37	Pain relief (4-point scale)
Mills, 1973	Randomised double blind, crossover	4	K (150 mg) I (1200 mg)	2 weeks	RA	34 34	12/22	Pain index (4-point scale)
Montrone, 1979	Randomised double blind, crossover	3	K (200 mg) I (1200 mg)	10 days	RA	53 53	15/40	Pain intensity (4-point scale)
Robbins, 1990	Randomised double blind parallel group	3	K (150 mg) I (1800 mg)	7 days	Traum. injuries	77 76	95/70	Percentage of responders (Pain relief score)
Saxena, 1978	Randomised parallel group	2	K (200 mg) I (1200 mg)	3 months	RA/OA	18 20	10/8 14/6	Total symptom rating score (0–4 point scale)

K: ketoprofen; I: ibuprofen; F: fenoprofen; N: naproxen; RA: rheumatoid arthritis; OA: osteoarthritis. §loading dosage.

Table II. Characteristics of the RCTs comparing ketoprofen *vs*. diclofenac.

Author, year	Study design	Jadad score	Treatment group dose/day	Treatment duration	Type disease	No. of patients	Sex M/F	Outcome measures used for meta-analysis
Matsumo, 1981	Randomised double blind parallel group	2	K (150 mg) D (75 mg)	2 weeks	Muscular pain	77 78	nd	Percentage of improved patients
Boey, 1988	Randomised parallel group	3	K (100 mg) D (75 mg)	3 months	RA	9 9	nd	Severity of pain (1–5 point scale)
Hynninen, 2000	Randomised double blind parallel group	3	K (100 mg) D (75 mg In (100 mg) Placebo	Single dose)	Post-operative pain	28 28 27 31	24/4 20/8 21/6 28/3	Pain intensity (VAS scale))
Cherubino 1997	Randomised double blind parallel group	4	K (150 mg) D (150 mg) Placebo	10 days	Low back pain	10 10 10	3/7 2/8 6/4	Pain intensity (VAS scale)
Tai, 1992	Randomised double blind double dummy parallel group	4	K (200 mg) D (100 mg)	1 week	Post-operative pain	25 25	12/14 12/14	Pain (VAS scale)

K: ketoprofen; D: diclofenac; In: indomethacin; RA: rheumatoid arthritis.

errors and standardised mean difference, statistically by rank correlation coefficients (Spearman and Kendall) and by a weighted linear regression of SMD on its Standard Error (SE) with weights equal to 1/SMD Variance (32-34); $p<0.05$ was considered significant.

Results
Study selection
Of the 62 papers identified by means of the key word and hand search, seven were duplicate and thirty were excluded after examining their abstracts. After further evaluation, twelve of the remaining 25 papers were excluded. Figure 1 shows the flow chart of the process of selection.

The meta-analysis was therefore based on 13 articles comparing ketoprofen with ibuprofen (eight RCTs) (9, 22-28) or diclofenac (five RCTs) (17-21).

Characteristics of the studies included in the meta-analysis
Tables I and II show the characteristics of the 13 RCTs included in the meta-analysis, four of which had a crossover design. The 13 RCTs involved a total of 898 patients: 522 treated with ketoprofen and 522 in the pooled control group treated with ibuprofen or diclofenac (9, 17-28).

Nine of the 13 RCTs included 544

Fig. 2. Summary assessments of risk of bias. Risk of bias summary.

Fig. 3. Meta-analysis of analgesic efficacy: size effect of ketoprofen *vs.* ibuprofen/diclofenac.

patients with systemic rheumatic diseases such as RA, OA, ankylosing spondylitis (AS), low back pain or painful shoulder (17, 18, 20, 22-24, 26-28), two patients with post-operative pain (19, 21), one patients with dysmenorrhea (25), and one patients with traumatic sports injuries (9).

The ketoprofen doses ranged from 150 to 200 mg, the ibuprofen doses from 800 to 1800 mg, and the diclofenac doses from 75 to 150 mg. Treatment duration ranged from a single dose to three months.

Changes in pain evaluated by a VAS or point scale were available for nine studies involving a total of 363 patients treated with ketoprofen and 362 treated with ibuprofen/diclofenac (9, 18-21, 24-27).

The change in the total symptom rating score was available for one study of 18 patients treated with ketoprofen and 20 treated with ibuprofen (28). Joint index changes were available for one study of 52 patients treated with ketoprofen and 50 treated with ibuprofen (22). The percentage of improved patients was available for two studies of
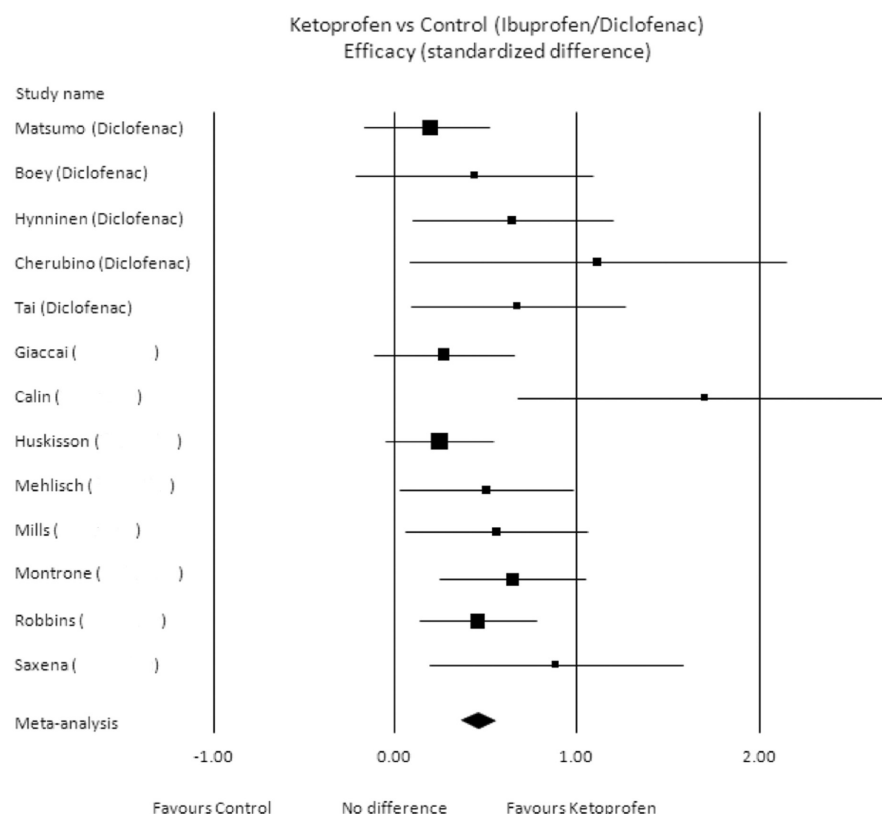
89 patients treated with ketoprofen and 90 treated with ibuprofen or diclofenac (17, 23).

Ten of the RCTs had a Jadad quality score of ≥3 (9, 18-22, 24-27). Quality assessment item have been summarised in Figure 2.

Meta-analysis of the efficacy of ketoprofen vs. ibuprofen/diclofenac

Figure 3 shows the size effect of ketoprofen and ibuprofen/diclofenac (pooled data).

The results of the meta-analysis showed a statistically significant difference in efficacy in favour of ketoprofen *vs.* ibuprofen and/or diclofenac. The meta-analysis was statistically significant (0.459, 95% CI 0.33-0.58; *p*=0.00) at all point-estimates of the mean weighted size effect in favour of ketoprofen (Fig. 3) *versus* ibuprofen/diclofenac. The test of heterogeneity for the efficacy outcome was not statistically significant (χ^2=18.07, df=12, *p*=0.1136, I^2=33.6%) (Table III).

Concerning the estimated efficacy outcomes, ketoprofen was superior to ibuprofen/diclofenac in all of the 13

RCTs, reaching a statistically significant difference (*p*<0.05) in nine studies (9, 19-21, 23, 25-28).

Analysis of the individual RCTs showed that four trials did not show any statistical difference in efficacy between ketoprofen and ibuprofen/diclofenac (17, 18, 22, 24). The trend in the point-estimates was slightly in favour of ketoprofen, but the 95% CIs were wide enough to include values in favour of the controls.

Meta-analysis of the efficacy of ketoprofen vs. ibuprofen

The eight studies comparing ketoprofen with ibuprofen involved a total of 531 patients (373 treated with ketoprofen and 372 with ibuprofen) (9, 22-28). The results of this further sub-analysis comparing ketoprofen with ibuprofen were similar to those of the pooled analysis, and showed that ketoprofen was significantly superior in terms of efficacy (mean = 0.475; 95% CI 0.32-0.62; *p*=0.0000, Fig. 4). The test of heterogeneity for the efficacy outcome was not statistically significant (χ^2=11.17, df=7, *p*=0.0951, I^2=37.3%).

Table III. Study summaries and Meta-analysis results.

Author	Ketoprofen versus	Ketoprofen			Control			Standardised Difference	95% C.I.		*p*-value
		Mean	SD	n.	Mean	SD	n.		Lower	Upper	
Matsumo	Diclofenac	0.714	0.452	77	0.628	0.483	78	0.183	-0.136	0.502	0.2580
Boey	Diclofenac	1.600	2.800	24	0.400	2.500	17	0.439	-0.215	1.093	0.1823
Hynninen	Diclofenac	7.000	3.000	28	5.000	3.000	28	0.657	0.104	1.211	0.0209
Cherubino	Diclofenac	2.180	1.300	10	0.760	1.100	10	1.129	0.085	2.174	0.0356
Tai	Diclofenac	15.110	3.500	25	12.180	4.830	25	0.684	0.094	1.273	0.0240
Calin	Ibuprofen	14.000	3.450	52	13.000	3.880	50	0.271	-0.125	0.666	0.1780
Giaccai	Ibuprofen	0.833	0.373	12	0.167	0.373	12	1.727	0.697	2.757	0.0021
Huskisson	Ibuprofen	3.600	0.800	90	3.400	0.800	90	0.249	-0.047	0.545	0.0985
Mehlisch	Ibuprofen	3.020	1.400	37	2.340	1.200	37	0.516	0.043	0.989	0.0330
Mills	Ibuprofen	0.620	1.700	34	-0.360	1.700	34	0.570	0.073	1.066	0.0251
Montrone	Ibuprofen	0.460	0.364	53	0.220	0.364	53	0.655	0.258	1.051	0.0015
Robbins	Ibuprofen	0.792	0.406	77	0.579	0.494	76	0.470	0.145	0.794	0.0048
Saxena	Ibuprofen	3.620	3.800	18	0.660	2.600	20	0.899	0.199	1.599	0.0133
	Meta-analysis							**0.459**	**0.333**	**0.585**	**0.0000**

Heterogeneity: χ^2=18.07; df=12; *p*=0.1136: I^2=33.6%.

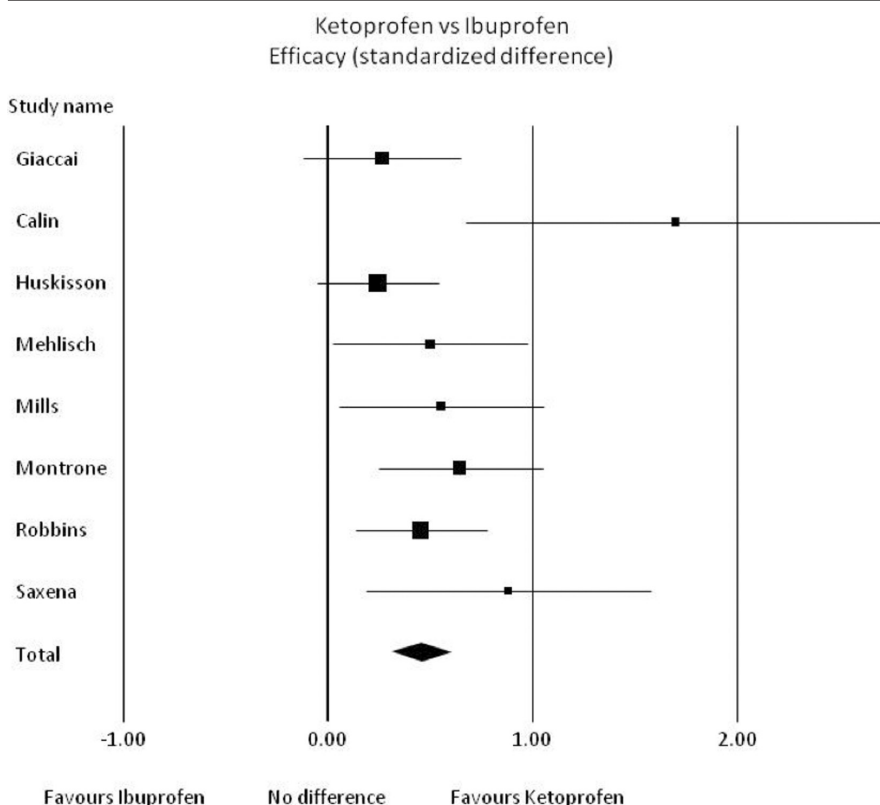*Meta-analysis of the efficacy of ketoprofen vs. diclofenac*

A total of 367 patients were included in the five RCTs comparing ketoprofen with diclofenac (149 treated with keto-profen and 150 treated with diclofenac) (17-21). These results confirmed the statistically significant difference in efficacy in favour of ketoprofen (mean = 0.422; 95% CI 0.19-0.65; *p*=0.0007,

Fig. 5) at all point-estimates of the mean weighted size effect (Fig. 4). The test of heterogeneity for the efficacy outcome was not statistically significant (χ^2=5.75, df=4, *p*=0.2190, I^2 = 30.4%).

Publication bias

The correlation between SMDs and Standard Errors (SE) is statistically

(*p*<0.01) significant both by Spearman (0.8462) and Kendall rank correlation coefficient (0.7179) (Fig. 6). As well as the weighted linear regression between SMDs and SEs is statistically (*p*<0.01) significant. These results are more related to the natural correlation between the SMDs and their SEs and to the low sensitivity of the former statistics in meta-analyses based on less than 20 trials than to a real publication bias (35).

Discussion

The multiplicity of currently available NSAIDs provides a strong rationale for comparing their risk/benefit ratios in order to help physicians make rational therapeutic choices for managing pain. Our meta-analysis compared the overall efficacy of ketoprofen with that of ibuprofen/diclofenac using data exclusively from RCTs with similar baseline demographic and disease characteristics. These NSAIDs were chosen because they are the most frequently prescribed for treating pain, and the outcomes were chosen because seem to be the most clinically relevant. The results showed that the effect of therapeutic doses of ketoprofen was mach greater than that of therapeutic doses of ibuprofen or diclofenac (9, 17-28). Furthermore, four studies (9, 20, 25, 28) also found that ketoprofen had an earlier onset of action than the other two drugs. In particular, the study of Cherubino *et al.* (20) showed a statistically significant difference in the onset
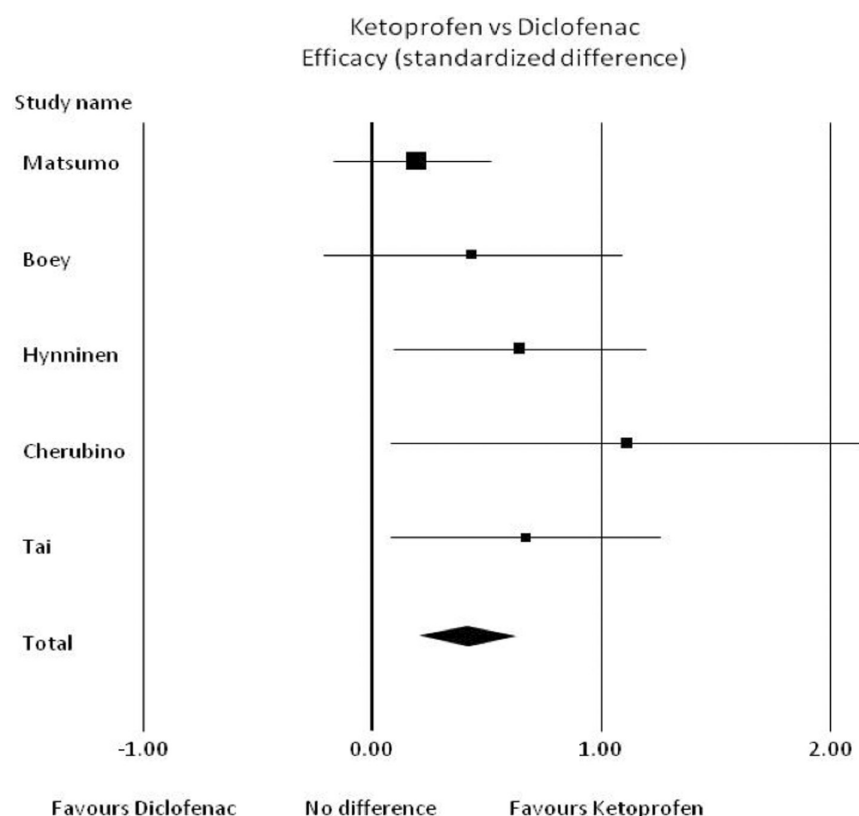

Fig. 4. Meta-analysis of analgesic efficacy: size effect of ketoprofen *vs*. ibuprofen.

Ketoprofen vs Diclofenac
Efficacy (standardized difference)

Fig. 5. Meta-analysis of analgesic efficacy: size effect of ketoprofen *vs*. diclofenac.

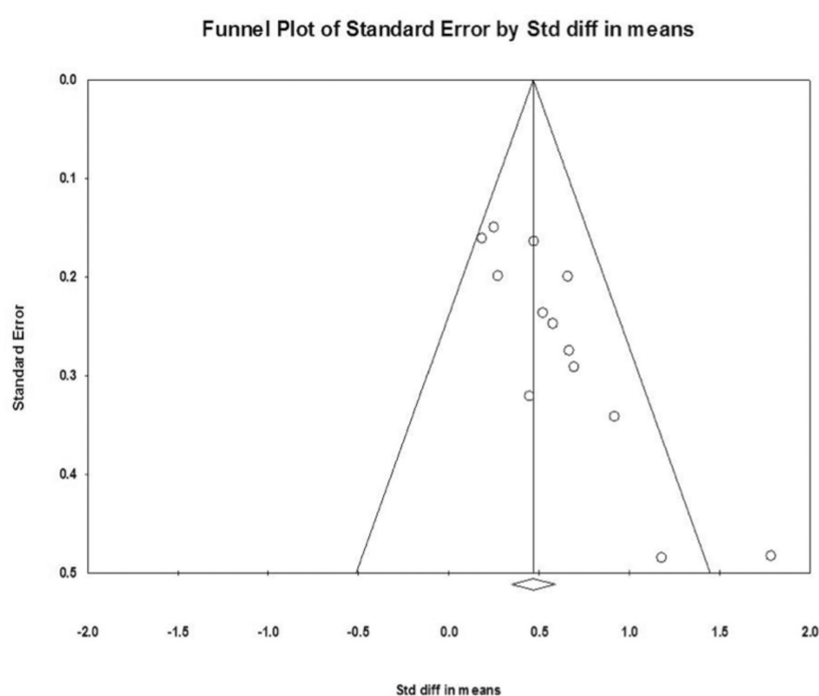### Funnel Plot of Standard Error by Std diff in means

Fig. 6. Funnel plot: SMD on SE.

of analgesic effect between ketoprofen and diclofenac.

The heterogeneity of the efficacy outcome was not different across the studies, thus guaranteeing the homogeneousness of the compared trials, and the reliability and validity of the results of the meta-analysis.

Our results indicate a statistically significant improvement in disease conditions in favour of ketoprofen, thus underlining its superior efficacy. This finding was also confirmed by the subanalyses that separately compared ketoprofen/diclofenac and ketoprofen/ibuprofen studies.

Our meta-analysis specifically evaluated the efficacy parameter of therapeutical doses as reccomended in clinical practice, but we are aware that it is very important, in particular when dealing with anti-inflammatory agents, to choose molecules based on the risk/benefit ratio. For this reason, even though no statistical evaluation was performed on this parameter, we clinically analysed the safety profiles described in the studies included in the meta-analysis and observed that, ketoprofen, ibuprofen and diclofenac appeared to be equally well tolerated and the adverse reactions to the three molecules were comparable and not serious. Moreover, it has been recently shown that dose of NSAIDs is very important, especially when evaluating gastrointestinal tolerability (29, 30), because the relative risk of gastrointestinal bleeding increases exponentially with higher doses of NSAIDs. The same therapeutical doses that we considered in our efficacy meta-analysis were evaluated in extensive safety analysis, confirming that ketoprofen, at these doses reccomended in clinical practice, has a good gastrointestinal tolerability, superimposable or even better than other NSAIDs, such as ibuprofen (29, 30). Taking this into account, particular attention to therapeutical doses, as we considered in our meta-analysis, is crucial in order to guarantee a good balance between efficacy and tolerability.

In conclusion, the strong evidence on the efficacy outcome, accordingly to an overall good safety profile, superimposable between the three molecules, underlines a better risk/benefit ratio for ketoprofen at the reccomended posology that should be taken into account by clinicians when dealing with patients affected from moderate to severe pain.

Study limitations

All of the trials included in the analysis had methodological limitations,

including unclear or inadequate allocation concealment and the absence of intention-to-treat (ITT) analyses. Furthermore, they differed in terms of treatment duration and efficacy parameters, even though the vast majority of them analysed pain outcomes. In order to limit the risk of publication bias, we did not limit the year of publication but decided to include all of the available trials in order to increase the value of the meta-analysis. Moreover, the relatively small number of studies (which may be considered another limitation) is consistent with the fact that only a few head-to-head trials have compared the efficacy of ketoprofen with that of ibuprofen or diclofenac, and further direct comparisons would be welcome in order to confirm these findings.

Despite these limitations, our meta-analysis has a number of strengths mainly based on the power and homogeneity of the statistical results. Furthermore, this is the first systematic analysis of all of the studies directly comparing the three drugs, which that are among the most widely used NSAIDs in clinical practice throughout the world.

Conclusion

Taken together, the findings of this meta-analysis show that ketoprofen is more efficacious than diclofenac/ibuprofen, and doctors should take this into consideration when choosing NSAIDs.

Acknowledgements

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