Original article

Safety of ketoprofen compared with ibuprofen and diclofenac: a systematic review and meta-analysis

Summary
Although several randomized controlled trials have examined the efficacy of different NSAIDs in head-to-head or placebo controlled design, few studies have specifically compared the safety and tolerability of the most commonly used NSAIDSs ketoprofen, ibuprofen and diclofenac. The main objective of this meta-analysis was to compare the safety of orally administered ketoprofen compared to ibuprofen and/or diclofenac. Studies including randomized controlled trials (RCTs) comparing the safety/tolerability of oral ketoprofen (100-200 mg/day) compared to ibuprofen (800-2400 mg/day) or diclofenac (75-100 mg/day) published on computerized databases (PubMed/Medline, Cochrane Central and Embase) were considered. A total of 10 RCTs involving 826 patients met the inclusion criteria: 3 comparing ketoprofen to diclofenac and 7 comparing ketoprofen to ibuprofen. Findings from this meta-analysis did not reveal any difference in safety for ketoprofen compared to ibuprofen and/or diclofenac. The difference between ketoprofen and the pooled ibuprofen/diclofenac data was not statistically significant (risk ratio; RR=1.02, 95% CI 0.78-1.233; P=0.92) at all point-estimates of the mean weighted size effect. Further sub-analyses also confirmed that ketoprofen was not significantly different to either diclofenac (RR= 0.86; 95% CI 0.51-1.45; P=0.58) or ibuprofen (RR= 1.08; 95% CI 0.79-1.48; P=0.65) at all point-estimates. Heterogeneity for the safety measures analyzed was not statistically significant for all meta-analyses. Findings from this meta-analysis demonstrate that the safety and tolerability of orally administered ketoprofen in patients treated for moderate-severe pain is similar to that of ibuprofen and/or diclofenac.

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Traditionally, non-steroidal anti-inflammatory drugs (NSAIDs) are used to treat patients requiring pain relief from acute and chronic conditions including rheumatoid arthritis (RA), osteoarthritis (OA), dysmenorrhea and post-surgical pain[1-4].Treatment with NSAIDs is widespread, due to an increase in the prevalence of pain-related and inflammatory diseases in the elderly population[5]. Following recent and numerous reports regarding adverse events associated with chronic administration of NSAIDs, major regulatory authorities (EMA and FDA) have recommended to use the lowest effective dose of these drugs for the shortest time necessary in order to control symptoms and attain therapeutic goals[6-8].For this reason, the careful evaluation of the benefit:risk ratio of different types of NSAIDs is essential.
Among the different NSAIDs available, ketoprofen, ibuprofen and diclofenac are still among the most frequent NSAIDs currently used, all three having been available for the past three decades[9-11]. All three anti-inflammatory agents have a similar mechanism of action, in that they inhibit both

constitutive and inducible forms of cyclooxygenase (COX1- and COX-2) resulting in the inhibition of prostaglandin E2 synthesis in addition to inhibition of the lipooxygenase pathway and in turn leukotriene production.[12] Although the efficacy of ketoprofen, ibuprofen and diclofenac has already been well documented in head-to-head RCTs[13-22], no study has specifically examined the safety and tolerability of these three NSAIDs together. Several meta-analyses have examined the safety and tolerabiity of NSAIDs, however, these studies included several other non-specific NSAIDs and anti-inflammatory drugs with different mechanism of action (e.g. selective COX-2 inhibitors)[23-27]. Although these large meta-analyses do provide important clinical insights into potential causal factors leading to the risk of developing gastrointestinal complications across a wide range of anti-inflammatory agents that are currently available, a lack of homogeneity between studies included and treatments compared, significantly hampers translation of these findings into everyday clinical practice.

Efficacy of ketoprofen versus ibuprofen and diclofenac

A recent meta-analysis of RCTs published by our group demonstrated that oral therapeutic doses of ketoprofen were significantly more effective than therapeutic doses of ibuprofen and diclofenac in relieving pain, raising questions about the comparative safety and tolerability profile of these three drugs[28].

The literature was systematically reviewed and search was restricted to RCTs comparing the efficacy of oral ketoprofen (50-200 mg/day) vs ibuprofen (600-1800 mg/day) or diclofenac (75-150 mg/day) published until June 2011. A total of 13 RCTs, including 898 patients, met inclusion criteria: 8 comparing ketoprofen vs ibuprofen and 5 comparing ketoprofen vs diclofenac. Nine of the 13 RCTs involved 544 patients with systemic rheumatic diseases such as arthritis rheumatoid (RA), osteoarthritis (OA), ankylosing spondylitis, low back pain or painful shoulder. The difference in efficacy between ketoprofen and ibuprofen/diclofenac was statistically significant (0.459, 95% CI 0.33-0.58; p=0.00) at all point-estimates of the mean weighted size effect. 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 9 studies[28].

Objective

In light of greater efficacy of ketoprofen, we decided to perform an extension of our previous efficacy meta-analysis in order to specifically evaluate the tolerability and the safety of orally administered ketoprofen vs ibuprofen and diclofenac and to obtain a complete comparative asses-

Table 1. Criteria for inclusion and exclusion of trials in meta-analysis.

Parameter	Criterion
Inclusion criteria	
Study design	Randomized controlled trial
Study population	Patients aged >18 years with moderate-to-severe pain
Dosage	50-200 mg/day for oral ketoprofen, 600-1800 mg/day for oral ibuprofen, 75-150 mg/day for oral diclofenac in accordance with recommended doses
Outcome measures	Number of patients who have experienced adverse events
Exclusion criteria	
Trial design	Studies not randomized or studies not examining safety/ tolerability
Treatment type	Studies not directly comparing ketoprofen with diclofenac or ibuprofen or those which comparing ketoprofen with diclofenac or ibuprofen combined with a narcotic or non-narcotic agent
Dosage and route of administration	NSAIDs not administered orally or administered at daily doses not within the above specified therapeutical ranges

sment of the risk-benefit profile of these commonly used NSAIDs.

Methods

Literature search

Meta-analysis was performed according to the PRISMA statement[29]. A systematic literature search was performed on the electronic databases Medline, Cochrane Central and Embase up to June 2011 to identify clinical trials comparing ketoprofen with ibuprofen or diclofenac. The search and selection is described in detail in a previous meta-analysis examining the efficacy of the three NSAIDs ketoprofen vs ibuprofen and/or diclofenac[28]. Each database was searched using various combinations of the key words: "clinical trial", "trial", "study", "ibuprofen", "Brufen", "diclofenac" "Voltaren", "Orudis", "OKi" and "ketoprofen". The literature search was extended by means of a hand search of references, and completed with abstracts of the Annual Scientific Meeting of the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) from 2009 to 2011.

Study selection

This systematic review was performed independently by two rheumatologists (PCSP and FA) in accordance with the Cochrane Collaboration guidelines[30]. Inclusion and exclusion criteria are presented in Table 1. Furthermore, retrospective studies were excluded to minimize heterogeneity, and reviews, letters, editorials, conference papers, case reports, basic science papers and clinical practice guidelines were not considered. Initially, the titles and/or abstracts of all identified trials were reviewed independently by two of the authors (PCSP and FA). This was followed by a second review of the eligible full-text publications using a recognized method of positive inclusion. Disagreement regarding the inclusion of articles was resolved by discussions with all authors.

Study quality assessment

Quality of selected publications was assessed using the Jadad's RCTs assessment scale[31], which assesses blinding, randomization and dropouts/withdrawn patients. Scale scores ranged from 0 to 5, with higher scores indicating less likelihood of bias in the results and a score of ≥3 indicates high quality. However, we also assessed articles with a Jadad score of <3 because of the limited number of studies comparing ketoprofen with the two other NSAIDs. According to the Cochrane Handbook Guidelines for the assessment of risk of bias[30], clinical trials were graded by 2 of the investigators (PCSP and FA) as previously described[28].

Data extraction and outcome definition

Data were extracted using a predefined data extraction form. The extracted information included the first author, year of publication, study design, Jadad quality score, type of disease, number of patients and controls, type of NSAIDs and dose, treatment duration and the mean age/gender ratio. In addition to collecting data on efficacy parameters[28], we also collected data on the number of patients with at least one adverse event (AE) reported by treatment group. Data reporting the severity and/or type of AE was not available in the majority of studies and was therefore excluded from analysis.

Statistical analysis

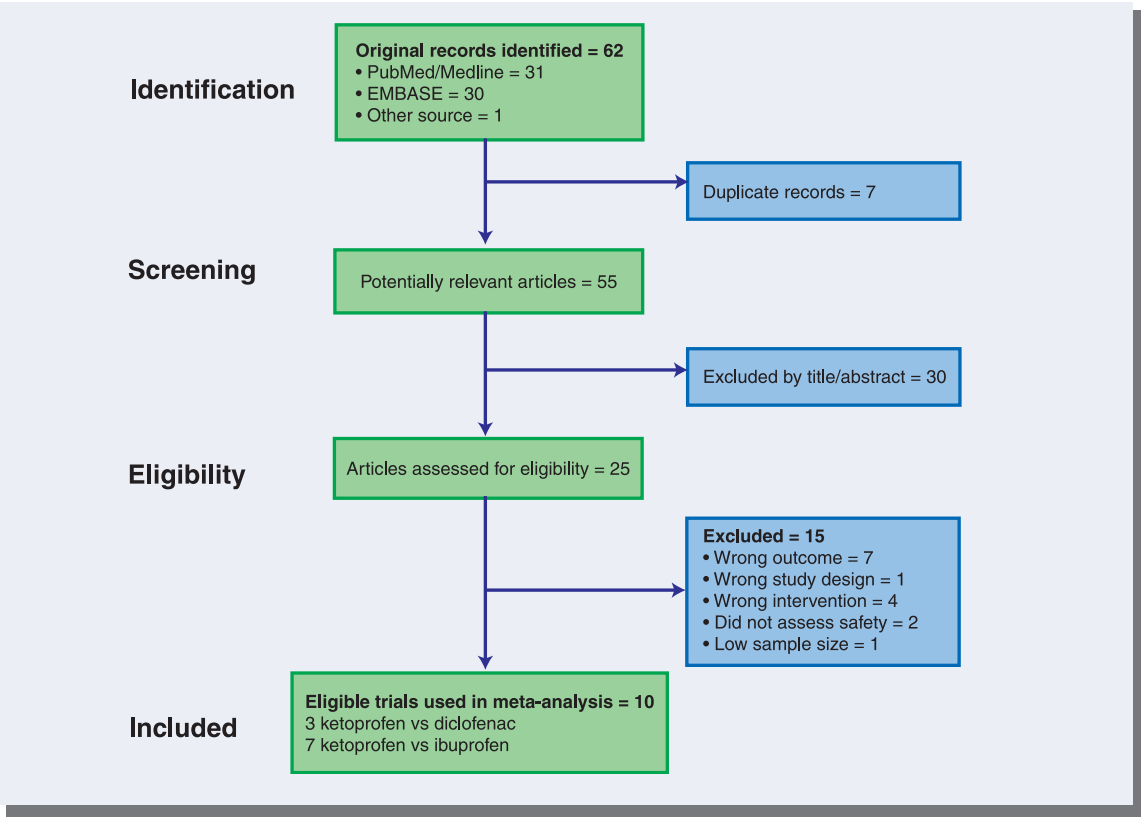
Denominators used for calculating the rate of AEs of each treatment group were reported in original papers as eligible patients after randomization and according to the intent-to-treat population. The association between exposure (treatment type) and binary outcome variables (number or % of AEs) was measured by relative risk and expressed as risk ratio (RR). Heterogeneity between studies was assessed using Cochrane's Q statistic[32-33], which was distributed as a χ^2 statistics. A P-value = 0.10 was used to indicate a lack of homogeneity among effects. I^2 statistics were also provided to quantify the percentage of total variation across studies attributable to heterogeneity, rather than by chance alone. Publication bias was assessed graphically using funnel plots of standard errors, statistically by rank correlation coefficients (Spearman and Kendall) and by a weighted linear regression of SMD on its standard error with weights equal to 1/standard error[34-36]. A p-value of <0.05 was considered statistically significant. All analysis was performed using BMDP software version 7.1 (BMDP Statistical Software Inc., Los Angeles, CA, USA).

Results

Study selection

Figure 1 shows a flow diagram of the selection process. Our initial search returned 61 distinct results, of which 25 were relevant based on rea-

Figure 1. Selection process for studies included in the meta-analysis.



ding their title and abstract. A further 15 studies were excluded because they had wrong outcome measures, wrong design, did not assess safety or were underpowered. Ten RCTs met the selection criteria and were included in the final meta-analysis. Three trials compared ketoprofen with diclofenac[13-15] and 7 compared ketoprofen with ibuprofen[16-22].

Characteristics of studies included in the meta-analysis

Characteristics of the ten studies included in the meta-analysis are presented in Table 2. All studies were randomized, double-blind and conducted between 1973 and 2000 (**Table 2**). These 10 RCTs involved a total of 826 patients (50% male): 413 treated with ketoprofen, 282 with ibuprofen and 131 with diclofenac. Of the 62 papers identified by means of the key word and hand search, 7 were duplicates and 30 were excluded after abstract evaluation. Five of the 10 RCTs included patients with systemic rheumatic diseases such as RA or OA[16,17,19,20,22], two of the studies included patients with post-operative pain[14,15], one study incuded patients with low back pain or painful shoulder,[13] one study incuded patients with dysmenorrhea[18], and one study included patients with traumatic sports injuries.[21] Ketoprofen doses ranged from 100 to 200 mg, ibuprofen doses from 800 to 2400 mg, and diclofenac doses from 75 to 100 mg. Treatment duration ranged from a single dose to three months. Seven of the RCTs included had a Jadad quality score of ≥3 [14-16,18-21] and mean Jadad quality score for all studies was 3.1±1.2.

Meta-analysis of the safety of ketoprofen vs ibuprofen/diclofenac

Figure 2 shows the size effect of ketoprofen and ibuprofen/diclofenac (pooled data). The results of the meta-analysis did not show any statistically significant difference in the risk of having an AE with ketoprofen vs ibuprofen and/or diclofenac (RR=1.02, 95% CI 0.78-1.33; P=0.92) (Table 3). The test of heterogeneity for safety measures was not statistically significant (χ^2=7.5; df=8; p=0.59; I^2=0%) (**Table 3**).

Meta-analysis of the safety of ketoprofen vs ibuprofen

The 7 studies comparing ketoprofen vs ibuprofen involved a total of 565 patients (283 treated

Table 2. Characteristics of RCTs and patients comparing ketoprofen to ibuprofen or diclofenac.

Author (year)	Ref.	Design type	Jadad score	Treatment group (dose/day)	Treatment duration	Disease type	No. of patients	Sex M/F
Matsumo (1981)	13	R, DB, PG	2	K (150 mg) D (75 mg)	2 weeks	Muscular pain	7778	n/a
Hynninen (2000)	14	R, DB, PG	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
Tai (1992)	15	R, DB, DD, PG	4	K (200 mg) D (100 mg)	1 week	Post-operative pain	25 25	12/14 12/14
Calin (1977)	16	R, DB, PG	4	K (150-300 mg) I (1200-2400 mg)	3 months	RA	52 50	23/29 22/28
Giaccai (1978)	17	R, DB, PG	1	K (160 mg) I (1200 mg)	3-15 days	OA	12 12	8/16
Mehlisch (1988)	18	R, DB, C	5	K (150 mg)§ I (800 mg)§	3 days	Dys-menorrhea	37 37	0/37
Mills (1973)	19	R, DB, C	4	K (150 mg) I (1200 mg)	2 weeks	RA	34 34	12/22
Montrone (1979)	20	R, DB, C	3	K (200 mg) I (1200 mg)	10 days	RA	53 53	15/40
Robbins (1990)	21	R, DB, DD, PG	3	K (150 mg) I (1800 mg)	7 days	Traum. injuries	77 76	95/70
Saxena (1978)	22	R, PG	2	K (200 mg) I (1200 mg)	3 months	RA/OA	18 20	10/8 14/6

C=Crossover; DB=Double Blind; DD=Double Dummy; PG=Parallel Group; R=Randomized
I=Ibuprofen; In=Indomethacin; K=Ketoprofen;
OA=Osteoarthritis; RA= Rheumatoid Arthritis
§ loading dosage; n/a=not available

Figure 2. Meta-analysis of relative risk of having an adverse event: risk ratio of ketoprofen vs ibuprofen/diclofenac. Data represented by Forest plot showing risk ratio and 95% confidence intervals.

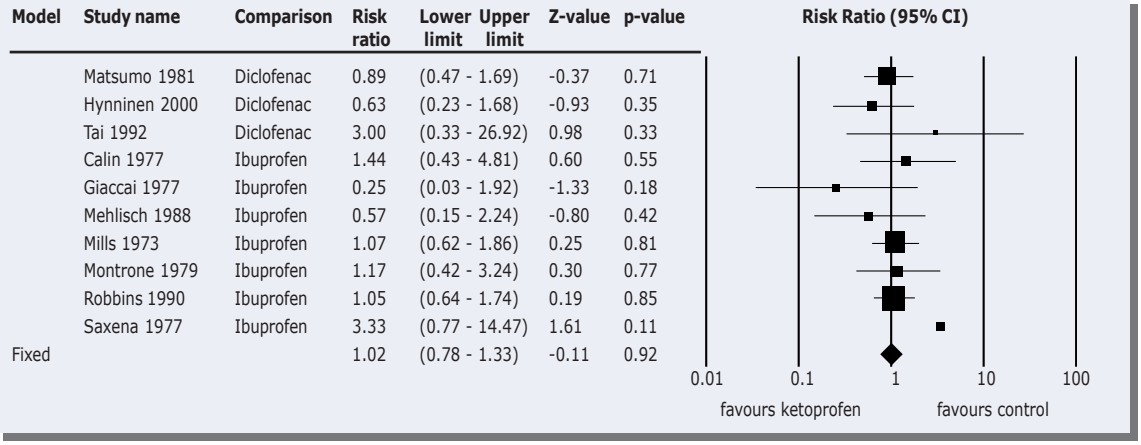


Table 3. Risk ratio for studies included in meta-analysis.

Author (year)	Ref.	Comparator	Risk ratio	Lower 95% CI	Upper 95% CI	Z-value	P-value
Matsumo(1981)	13	Diclofenac	0.886	0.465	1.689	-0.367	0.714
Hynninen (2000)	14	Diclofenac	0.625	0.233	1.677	-0.933	0.351
Tai (1992)	15	Diclofenac	3.000	0.334	26.919	0.981	0.326
Calin (1977)	16	Ibuprofen	1.442	0.433	4.808	0.596	0.551
Giaccai (1978)	17	Ibuprofen	0.250	0.033	1.923	-1.332	0.183
Mehlisch (1988)	18	Ibuprofen	0.571	0.146	2.236	-0.804	0.421
Mills (1973)	19	Ibuprofen	1.071	0.617	1.860	0.245	0.806
Montrone (1979)	20	Ibuprofen	1.167	0.420	3.241	0.296	0.768
Robbins (1990)	21	Ibuprofen	1.051	0.635	1.740	0.192	0.848
Saxena (1978)	22	Ibuprofen	3.333	0.768	14.471	1.607	0.108
Fixed model			**1.015**	**0.775**	**1.329**	**0.106**	**0.915**
Heterogeneity		χ^2=7.5; df=8; p=0.59; I^2=0.0%					

with ketoprofen and 282 with ibuprofen)[16-22]. The results of this further sub-analysis comparing ketoprofen vs ibuprofen were similar to those of the pooled analysis, in that ketoprofen was not significantly different to ibuprofen (RR=1.08; 95% CI 0.79-1.48; P=0.65; Figure 3). Also in this sub-analysis, the test of heterogeneity for safety measures was not statistically significant (χ^2=5.3; df=5; p=0.5; I^2=0%).

Meta-analysis of the safety of ketoprofen vs diclofenac

A total of 261 patients were included in the 3 RCTs of ketoprofen vs diclofenac (130 and 131

Figure 3. Meta-analysis of relative risk of having an adverse event: risk ratio of ketoprofen vs ibuprofen. Data represented by Forest plot showing risk ratio and 95% confidence intervals.

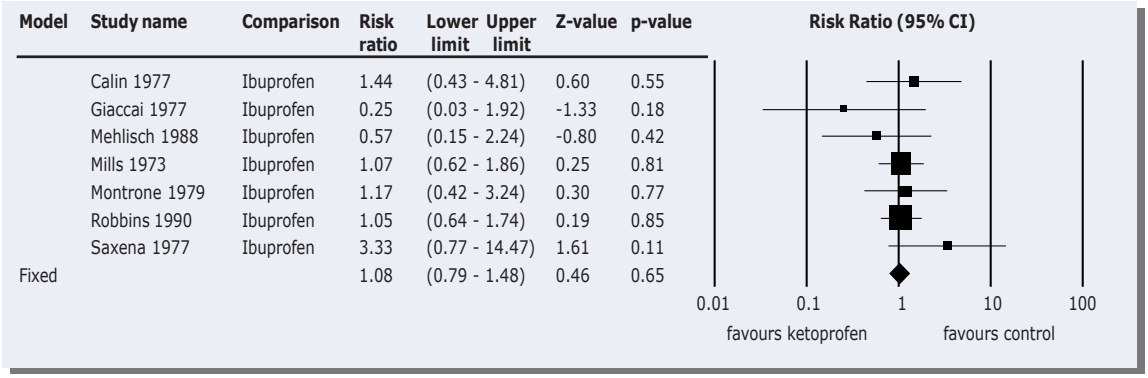


Figure 4. Meta-analysis of relative risk of having an adverse event: risk ratio of ketoprofen vs diclofenac. Data represented by Forest plot showing risk ratio and 95% confidence intervals.

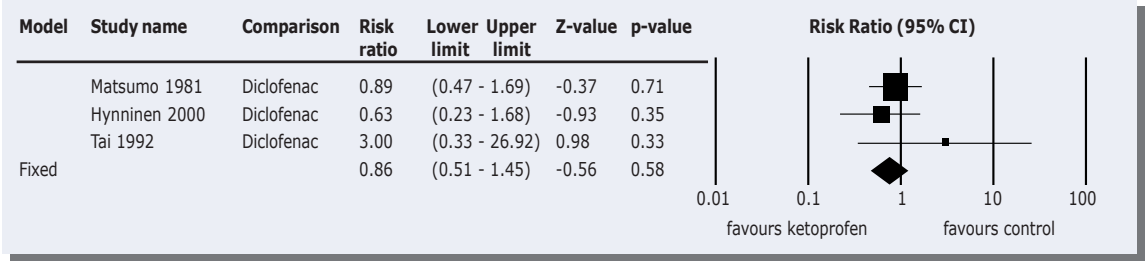
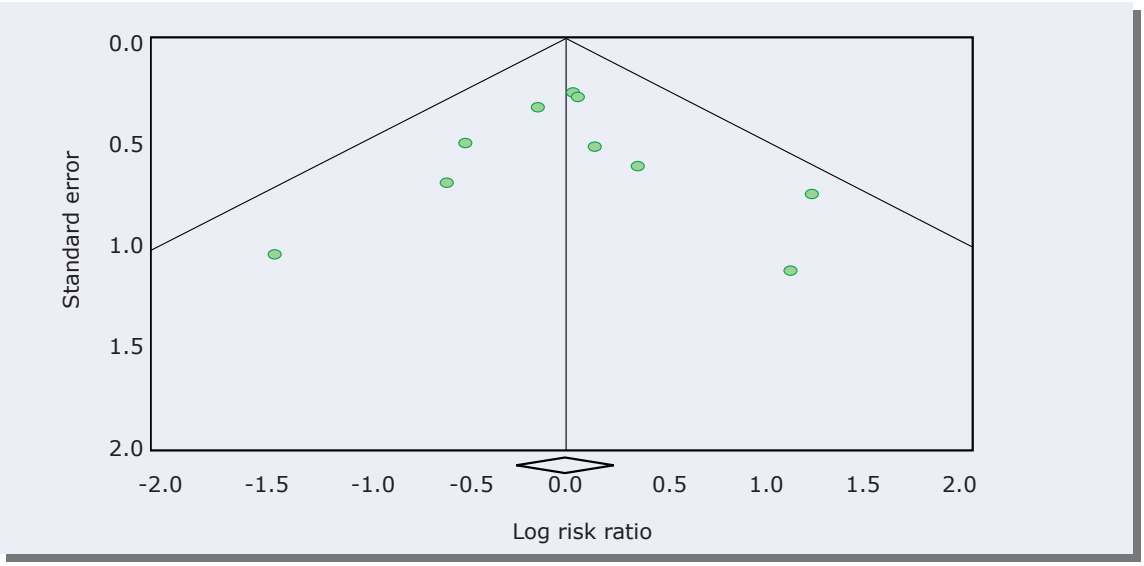


Figure 5. Funnel plot of standard error by log risk ratio of all 10 studies.



treated with ketoprofen and diclofenac, respectively).[13-15] Findings from this analysis indicate a slight favor towards ketoprofen treatment over diclofenac (RR=0.86; 95% CI 0.51-1.45; P=0.58), equating to an approximately 14% reduction in risk of AE for ketoprofen (Figure 4). The test of heterogeneity for the safety outcome was not statistically significant (χ^2=1.66; df=1; p=0.44; I^2=0%).

Publication bias

The association between standard error (SE) and risk ratio was not statistically significant (Kendall correlation coefficient=0.13, Z value=0.54; p=0.59), indicating that publication bias was not a problem in this meta-analysis (**Figure 5**).

Discussion and conclusion

The main findings from the present meta-analysis demonstrate that in patients treated for moderate-severe pain, the risk of having an AE is similar, whether they are treated orally with ketoprofen, ibuprofen or diclofenac. These findings provide an important adjunct to our previous meta-analysis, where we have demonstrated superior efficacy offered by ketoprofen over ibuprofen or diclofenac[28], thereby facilitating rheumatologists and related medical specialists alike with a comprehensive viewpoint when confronted with decision on choice of therapy among these and other NSAIDs. Although ketoprofen, ibuprofen and diclofenac have been extensively used for the past 30 years or so, these older generation NSAIDs are still frequently used[9-11]. Due to the much publicized hepatotoxicity warnings in Europe in relation to nimesulide[37], a reduction in the consumption of this drug (approximately 40%) was observed between 2007 and 2008 and a consequent increase in the use of other over-the-counter NSAIDs, particularly ketoprofen (+52%), ibuprofen (+57%), and diclofenac (+18 %)[38]. With this in mind, the availability of efficacy and safety data on these NSAIDs has been particularly important for physicians in making rational therapeutic choices in pain management. Our meta-analysis compared the overall tolerability of ketoprofen versus ibuprofen/diclofenac using data that was derived exclusively from RCTs, with similar baseline demographic and disease characteristics[13-22]. These specific NSAIDs were chosen because they are the most frequently prescribed in Europe for treating pain, and the frequency of AEs was chosen as they were easily accessible and reflect global safety profile of each drug. The heterogeneity for tolerability outcome measures was not different across the studies and this guaranteed that the compared trials were homogeneous and that meta-analysis results were reliable and valid. Both the pooled analysis and sub-analyses demonstrated that the risk of having an AE was similar in patients administered ketoprofen compared to ibuprofen or diclofenac. Our findings corroborate with a large clinical trial on 11,245 patients examining the tolerability of ketorolac, diclofenac and ketoprofen in patients after major surgery, in that all three NSAIDs had a similar frequency of AEs[39]. In contrast, several meta-analyses consistently show reduced risk of

an AE (predominantly upper gastrointestinal complications) for ibuprofen over diclofenac and ketoprofen[23-27]. This has been explained in part by the fact that ibuprofen was often administered at low doses in these studies, whereas ketoprofen was frequently (>80% of cases) taken greater than the maximum recommended dose of 200 mg/day[24]. Since it has already been established that dosage of NSAIDs is important in the evaluation of gastrointestinal tolerability[40-42], the relative risk of gastrointestinal bleeding correspondingly increases with higher doses of NSAIDs. For this reason, use of the therapeutic dosage, as considered in the present meta-analysis, is extremely important for striking the correct balance between efficacy and tolerability.

It is obvious that choice and dose of NSAID alone cannot predict risk of upper gastrointestinal bleeding/perforation and other factors should be considered. The clinical background, (for example previous history of peptic ulcer or its complications) and the use of concomitant medications or a possible genetic susceptibility, all play a role in determining the final absolute risk in an individual[26,43].

Several trials included in the present meta-analysis had methodological limitations, namely unclear or inadequate allocation concealment and the absence of intention-to-treat analyses. Furthermore, trials differed in terms of treatment duration and disease type. Our analysis was limited by the fact that we did not stratify by type and/or severity of AEs, due to disparity in the availability of this information across the different studies. Publication bias was limited by the fact that we did not limit the year of publication but decided to include all available trials. Moreover, the relatively small number of included studies (n=10), which could be considered another limitation, is consistent with the fact that only a few head-to-head trials have been performed comparing the safety of ketoprofen versus ibuprofen or diclofenac. However, despite these limitations our meta-analysis has several strenghts, particularly the power and homogeneity of the statistical results. Furthermore, this is the first systematic analysis of all studies that directly compare these three drugs, that are among the most frequently used NSAIDs worldwide in clinical practice.

Findings from the present meta-analysis indicate that the safety and tolerability are similar between ketoprofen, ibuprofen and diclofenac. Based on findings from our recent meta-analysis showing superior efficacy for ketoprofen over the other two NSAIDs, our present findings support the use of ketoprofen over diclofenac or ibuprofen for the treatment of moderate-severe pain.

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Authors' contributions

All authors collected clinical data and evaluated the manuscript. FA and PS-P analyzed and interpreted data. CGE wrote the manuscript. All authors were involved in drafting the manuscript and read and approved the final version of the manuscript.

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Competing interests

FA and PS-P have received consultancy fees or congress invitations from Dompe' SpA, Italy. TiM

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