Antipyretic Effect of Oral Dipyrone (Metamizole) Compared to Oral Ibuprofen in febrile Children: A Systematic Review and Meta-Analysis

Maged Alnajar
magedalnaggar@gmail.com
Al-Hikma University
Zahraa Saker
Lebanese University
Fatma Haji
Cario University
Menna Abdelsamed
Beni-Suef University
Zeinab Khaled
Cario University
Mohamed Abd-ElGawad
Fayoum University

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Abstract

Background

The nonsteroidal anti-inflammatory medication dipyrone (metamizole) is most frequently used as a painkiller as well as an anti - pyretic. Despite the fact that it has been banned in many high-income countries following confirmed studies of fatal agranulocytosis and adverse drug reactions, it is still widely used in various countries of the world. However, the antipyretic therapeutic indications of dipyrone in febrile children are currently unknown, and there is little information on the advantages and disadvantages of using dipyrone in febrile youngsters. In febrile youngsters, we expected that dipyrone's antipyretic effectiveness wouldn't be any more effective than ibuprofen. Therefore, the purpose of this research is to evaluate the effectiveness of oral dipyrone and oral ibuprofen as antipyretics in febrile children.

Methods

Several databases, including PubMed, Scopus, Web of Science, and Cochrane Library, were searched thoroughly using a pre-established search strategy for potential research. The studies included in this analysis comprised randomized controlled trials that compared the antipyretic effects of oral ibuprofen and oral dipyrone in febrile kids. Data analysis was carried out using Revman 5.4 software.

Results

Three studies were selected among the 27 publications we discovered to be applicable, and they underwent qualitative and quantitative analysis. The pooled analysis revealed no discernible difference between oral dipyrone and oral ibuprofen in terms of their antipyretic effects (Mean difference (MD) = 0.06; 95% confidence interval (CI): -0.08, 0.20).

Conclusion

Both oral dipyrone and ibuprofen are effective in reducing high-temperature levels in febrile children without any significant difference.

Background

The most frequent problem in pediatric treatment is fever. Being the cause of around 25% of consultations in emergency and primary care departments, it needs careful investigation (1–3). It is often described as having a core temperature of at least 38°C with significant variations at other measurement locations, such as the rectum, axilla, skin, mouth, and ear (4). Noteworthy that the accurate site for temperature measurement and the appropriate measuring device remain a matter of debate in the pediatric population (5). Yet, clinical examination, investigation of laboratory findings, and administration of appropriate antipyretic drug remain the cornerstone of safe fever management in children (6).

Many antipyretic drugs with different modes of action are recommended to decrease the temperature in children (7) such as nonsteroidal anti-inflammatory drugs (NSAIDs) and paracetamol (acetaminophen) (8). As these drugs are widely used as antipyretics, they appear to be safe; but there are still controversial results regarding the development of adverse side effects (8). As adverse side reactions are uncommon, they are more likely to develop in NSAIDs than in paracetamol (8).

Dipyrone, or metamizole, belongs to NSAIDs and is usually administrated orally or parenterally as an analgesic and antipyretic drug (8). Dipyrone is still regarded as a well-liked analgesic and antipyretic medicine in spite of the contentious studies about the benefit-risk ratio of the treatment (9–11). Due to its connection to severe and sometimes deadly adverse medication responses such agranulocytosis and anaphylactic reactions, it was outlawed in the United States and other European nations. (12). However, it is still frequently used in practice guidelines for perioperative pain and fever management in many other countries in Europe, Australia, and Asia (13, 14).

Ibuprofen, which also belongs to the NSAIDs, has been prescribed as an analgesic for acute and chronic pain and inflammatory conditions with a favorable overall safe profile (15, 16). The American Academy of Pediatrics recommended using it as an antipyretic in children who were feverish. (17). It shows a strong antipyretic effect with a long duration of temperature reduction; however, its administration must be monitored to avoid side effects (15).

As the antipyretic therapeutic indication of dipyrone in febrile children are still unclear, and the data of both the benefits and risks of dipyrone use in febrile children are scarce. In febrile youngsters, we expected that dipyrone's antipyretic effectiveness wouldn't be any greater than ibuprofen's. To evaluate the antipyretic effectiveness of oral dipyrone to oral ibuprofen in febrile children, we plan to examine, compile, and analyze all relevant randomized clinical trials (RCTs).

Method

Study design and registration:

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) and Cochrane Handbook of Systematic Reviews of Intervention (Cochrane) were used to conduct this meta-analysis (18, 19). The following were the components of the research question in the PICO form:

- Population: children that are febrile
- Intervention: Oral dipyrone
- Comparison: Oral ibuprofen
- Outcome: A drop in temperature

Eligibility criteria and studies’ selection:

The following were the main eligibility requirements for inclusion, according to the PICO of this study: A pediatric population under the age of 18, feverish children, medication comparison including at least one dosage each of oral dipyrone and oral ibuprofen, and (d) RCTs evaluating the antipyretic effects of both drugs in febrile children. On the other side, this research excluded reviews, book chapters, theses, editorials, letters, conference papers, articles written in languages other than English, animal or in vitro studies, cohort studies, case-control studies, non-clinical investigations, and meta-analyses. Additionally, data that was unreliable or inadequate for extraction was eliminated. Dosage and gender did not support exclusion. The titles, abstracts, and full texts of the publications acquired from various electronic databases were scrutinized for eligibility.

Literature search:

Between March 1974 and April 2022, the Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, Scopus, and Web of Science databases were mostly used to find potential research. The terms "dipyrone and ibuprofen, and youngsters" were among the relevant ones. Each core element and the search portions were connected and combined using the Boolean operators "OR" and "AND," respectively. The supplemental file has a thorough search plan (Appendix 1). To weed out pointless research, each author separately reviewed the titles and abstracts. Retrieving and carefully reviewing the remaining papers. The qualifying requirements led to the articles' exclusion.

Data extraction and quality assessment:

Based on information on trial designs, participant characteristics, diagnostic fever measurement, kind of antipyretic medicine (dipyrone and ibuprofen), and result, the authors independently retrieved the data. All writers discussed the final replies, and any disagreements were resolved. For the purpose of assessing the caliber of the chosen RCTs, the Cochrane Risk-of-Bias Tool for Randomized Trials (ROB1) was utilized. The six areas of the ROB1 tool include the randomization procedure, deviations from planned interventions, missing outcome data, outcome measurement, choice of the reported result, and additional biases. The evaluations of the assessors were divided into three categories: high, low, and uncertain risk of bias. The writers separately assessed the six domains for each research. The replies were then considered by all the writers, and any disagreements were settled (20).

Outcome definition:

The antipyretic efficacy of dipyrone and ibuprofen was evaluated mainly by the mean change of baseline temperature at 30, 45, 60, and 120 minutes after drug administration. The baseline temperature was between 38.0 and 40.5°C. Time and rate of temperature reduction, maintenance of non-febrile state, safety, and tolerability outcomes were also assessed.

Data synthesis and assessment of heterogeneity:

For the statistical studies, Revman software version 5.4 was employed. For continuous data, the mean difference (MD) and standard deviation (SD) were combined with 95% confidence intervals (CI). I-squares that were heterogeneous were above 60%.

Results

Our search turned up a total of 1489 entries across all search databases, including 160 records from PubMed, 1109 recordings from Scopus, 152 records from Web of Science, and 68 records from the Cochrane Library. 254 of them were eliminated due of duplicates. 1209 records were removed after title and abstract screening because they were unnecessary. The eligibility of the remaining 27 records' entire texts was checked. A further 24 records were removed from this group of 27 publications because they did not contrast the antipyretic effects of oral dipyrone with oral ibuprofen. Finally, this systematic review and meta-analysis comprised three randomized clinical trials. The PRISMA flowchart is shown in Fig. 1.

Characteristics of the included studies:

547 febrile children were enrolled in the three included RCTs from Brazil, Argentina, Chile, Mexico, and Peru. The RCTs in question were released between 2001 and 2011. The median age ranged from 16.3 to 29 months based on the statistics that were made available. Without receiving a concurrent treatment modality, 275 individuals got oral ibuprofen and 272 patients received oral dipyrone. 38°C to 38.5°C was the stated range for the baseline temperature. The RCTs that were included have their demographic details compiled in Tables 1and 2.

Table 1: Summary table of the included randomized clinical trials

Author	Country	Treatment	Gender (M/F)	Age (months)	Tympanic temperature (°C)	Nb of Adverse event(s)
Wong et al. 2001 (21)	Brazil, Argentina, Mexico and Chile	Dipyrone 15 mg/Kg	128/81	28±18	39.3±0.6	3
		Ibuprofen 5 mg/Kg for <39.2°C and 10 mg/Kg for ≥39.2°C	118/91	29±19	39.2±0.6	2
Prado et al. 2006 (22)	Peru	Dipyrone 15 mg/Kg	11/13	16.3±13.7	38.8±0.4	12
		Ibuprofen 10 mg/Kg	12/13	17.9±12	39.0±0.5	10
Magni et al. 2011 (23)	Brazil	Dipyrone 5 mg/Kg	39	27±20	39.6±0.4	1
		Ibuprofen 10 mg/Kg	41		39.5±0.3	2

M/F: male to female ratio

Table 1
Summary of included studies key features

Study ID	Title	Study design, country, and timing	Criteria	Sample size	treatment regimen	Control group	study duration
Anthony Wong et al, 2001	**Antipyretic Effects of Dipyrone Versus Ibuprofen Versus Acetaminophen in Children: Results Multinational, Randomized, Modified Double-Blind Study**	Randomized, modified double blind study/Multinational (Brazil, Argentina, Chile, Mexico)/May to December, 1998.	• Young children with fever from the age of 6 months to 6 years old.	418 patients (209 for oral dipyron, and 209 for oral ibuprofen)	N = 209 participants received Single dose of oral dipyrone(Novalgina) 15 mg/kg.	N = 209 Participants received Single dose of oral Ibuprofen(Ibupirac) was given based on initial temperature using a dose of 5 mg/kg for To < 39.20C and 10 mg/kg for To.39.20C.	8 months
Judith Prado et al, 2006	**Antipyretic effificacy and tolerability of oral ibuprofen, oral dipyrone and intramuscular dipyrone in children: a randomized controlled trial**	RCT single-blind /Peru/Feb to Jun,2003	• Young children with fever from the age of 6 months to 6 years old.	49 patients (24 for oral dipyron, and 25 for oral ibuprofen)	N = 24 Participants received single dose of oral dipyrone (15mg/kg)	N = 25 Participants received single dose of oral ibuprofen (10 mg/kg)	5 months
Ana Maria Magni et al, 2011	**Antipyretic effect of ibuprofen and dipyrone in febrile children**	Open label RCT /Brazil/Sep,2000 to Mar,2001	• Young children with fever from the age of 6 months to 8 years old • weight > = 6kg and < = 22kg • fever at least for 4 hours and up to 48 hours	80 patients (39 for Oral dipyrone and 41 for oral ibuprofen)	N = 39 participants received Single dose of oral dipyrone 15 mg/kg.	N = 41 Participants received Single dose of oral ibuprofen (10 mg/kg)	7 months

Table 1. Summary of the included studies. RCT: Randomized controlled trial. N: number.

Table 2. Baseline characteristics of enrolled patients in each included study**.** Data are expressed as mean and standard deviation (SD) or frequency and percentage.

Study ID	Groups	Number of patients	Age mean ± SD	Males (%)	Mean Baseline temperature	Weight (kg)	Race			
							White	Black	Asian	American Indian or Alaska Native
Anthony Wong et al ,2001	Oral dipyron 15mg/kg	209	28 ± 18	128 (61.2%)	39.3 ± 0.6	13 ± 4	209 (100%)	0	0	0
	Oral ibuprofen 10mg/kg	209	29 ± 19	118 (56.4%)	39.2 ± 0.6	13± 4	209(100%)	0	0	0
Judith Prado et al, 2006	Oral dipyron 15mg/kg	24	16.3 ± 13.7	11 (45.8%)	38.8± 0.4	10.1± 2.4	24 (100%)	0	0	0
	Oral ibuprofen 10mg/kh	25	17.9± 12	12 (48%)	39 ± 0.5	10.8±2.9	25 (100 %)	0	0	0
Ana Maria Magni et al, 2011	Oral dipyron 15mg/kg	39	27 ± 20	21 (53.8%)	39.6 ± 0.4	-	39 (100%)	0	0	0
	Oral Ibuprofen 10mg/kg	41	27 ± 20	23 (56.1%)	39.5 ± 0.3	-	41 (100 %)	0	0	0

Quality assessment:

The studies (21–23) that were included had a low overall risk of bias. Concerns were raised about the randomization process bias in two studies (21, 23) that reported using an insufficient randomization strategy. Due to the lack of sufficient information on the allocation concealment and randomization method, two research (21, 22) were deemed to raise some issues. Regarding participant and staff blinding, one research (23), which was single-blinded, was rated as having a high risk of bias, but the other two studies (21, 22) were rated as having a low risk of bias owing to adequate patient and examiner blinding. Regarding the evaluation of the results, one research (23) revealed a high risk of bias owing to missing data spanning various time periods, but the other two studies (21, 22) had a low risk of bias since they had enough data. The risk of bias in each of the three investigations (21–23) was minimal with respect to attrition and reporting bias. The risk of bias evaluation of the selected studies is shown in Figs. 2 and 3.

Temperature reduction:

The data of temperature decrease was obtained from the three selected RCTs (21–23). The resolution of temperature was measured at 30, 45, 60 and 120 min after oral administration of either dipyrone or ibuprofen. The pooled estimate of fever reduction revealed similar temperature decrease after 30 min of either dipyrone (203/413) or ibuprofen (210/413) administration by -0.03 (95% CI: -0.29, 0.24) with high heterogeneity between the two drugs (I^2 = 82%) **(**Fig. 4**)**. Fever resolution at 45 and 60 min post administration of these drugs also indicated a decrease in temperature by 0.08 and 0.03 with the absence of any significant difference between the two groups (95% CI: -0.01, 0.18 and − 0. 15,0.22) respectively **(**Figs. 5 and 6**)**. The pool estimate was low heterogeneous (I^2 = 0%) after 45 min but high heterogeneous (I^2 = 75%) after 45 and 60 min from the initial drug administration, respectively (21, 22). The results of the studies after 120 min of drug administration was also examined (21–23) where the pool estimate of fever reduction for the three RCTs demonstrated also similar antipyretic effect of both dipyrone (214/435) and ibuprofen (221/435) with 0.06 mean difference (95% CI: -0.08, 0.20). Yet, the pool estimate was slightly heterogeneous (I^2 = 30%) **(**Fig. 7**)**. Dipyrone and ibuprofen did not significantly reduce temperature at various time points following oral intervention, according to pool estimates, which were only extremely diverse at 30 and 60 min.

Safety and adverse effects:

Discontinuity was see in both groups mainly due to temperature elevation or therapeutic failure. Ibuprofen-associated adverse events were 3 cases of bronchitis and fever persistence. However, only one hypothermia case was associated with dipyrone (23). remarkably, other studies have reported similar frequencies of adverse events in the two groups (21, 22). The majority of the negative reactions were gastrointestinal in nature, including nausea, diarrhea and vomiting, respiratory distress, anorexia, hypo-activity and shivering.

Discussion

Numerous exogenous pyrogens and endogenous molecules cause fever, a common aftereffect of infection and an important factor of the host's defense mechanism (24). The appropriate management of high temperature in children requires adequate temperature measurement and precise use of antipyretic medications. Dipyrone is characterized by analgesic and antipyretic properties intending it to the clinical practice use in many countries; yet, it is panned in others due to some adverse effects (25) shedding light on its safety profile. Ibuprofen is commonly used drug for also its analgesic and antipyretic efficacies over different age groups (26). These two drugs had comparable safety profiles with regard to serious adverse effects, renal impairment, gastrointestinal hemorrhage, liver toxicity, and asthma (27).

The given pooled findings of this investigation did not reveal any appreciable significant differences in the antipyretic effectiveness of oral dipyrone compared to that of oral ibuprofen across various time intervals in the pediatric population, according to the available data. These results demonstrate that dipyrone and ibuprofen have comparable antipyretic effectiveness in febrile children. Dipyrone and ibuprofen's antipyretic effects have already been studied in observational studies and a randomized trial. Each one showed a peak temperature drop of around 1°C (28–30), which contrasts with the outcomes of previous clinical studies (21–23). The discrepancy in sample sizes across the studies and the vast range of patient ages might be to blame for the variation in the temperature decrease mean.

If no clinically significant improvement is seen two hours after treatment, the antipyretic therapy is declared ineffective (30). The peak of antipyretic activity is predicted to occur 2–4 hours after delivery when the recommended doses are employed, such as 15 mg/kg for dipyrone and 10 mg/kg for ibuprofen (21–23). Therefore, further antipyretic options should be researched if no effect is shown within this time frame.

Ibuprofen and dipyrone were linked to the bulk of the unfavorable gastrointestinal side effects, which included nausea and diarrhea (21). Weeping, anorexia, hypoactivity, shivering, and vomiting frequency were not different between the two groups, according to reports (22). Without any evidence to back it up, dipyrone-related risks for aplastic anemia and agranulocytosis have already been widely characterized (31). However, the elderly, in particular, who are on methotrexate therapy, had almost half of the dipyrone-associated agranulocytosis within the first 13 days following medication, indicating a significant need for drug-administration precaution (32).

Strength, limitations and conclusion:

This research is regarded as the pioneering meta-analysis on the effectiveness of ibuprofen and dipyrone. Four distinct database websites were used to get the information. Despite carefully compiling data from clinical studies, this research nevertheless had certain limitations. The low rate of temperature reduction and the limited sample size in the included trials made it difficult to compare the side effects of dipyrone and ibuprofen. Additionally, as both dipyrone and ibuprofen may be administered using a variety of methods, a conclusion about the best pharmaceutical administration approach could not be reached. Clinical studies comparing the effectiveness of oral dipyrone and oral ibuprofen as antipyretic medications provided useful evidence that dipyrone may not be superior to ibuprofen in febrile children. They both seem to have similar safety profiles and a generally low frequency of adverse effects. However, it is still unclear if aplastic anemia and agranulocytosis are dangerous; hence, large-scale randomized investigations are required.

Abbreviations

CI: Confidence interval

MD: mean difference

NSAIDs: nonsteroidal anti-inflammatory drugs

RCTs: Randomized controlled trials

SD: Standard deviation

Declarations

Conflicts of interest: Dr. Maged Alnajar has nothing to disclose. All the authors also declare no conflict of interest.

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Declaration of competing interest: The authors declare that there is no conflict of interests regarding the publication of this article.

Ethical approval: This article does not contain any studies with human participants or

animals performed by any of the authors.

Consent to participate: not applicable

Consent for publication: not applicable

Availability of data and material: All data generated or analyzed during this study are included in this published article or in the data repositories listed in References.

Code availability: not applicable

Authors contributions:

Maged Alnajar leads the team, performed the search strategy and data collection step, solved any conflict in the screening phase, performed the meta-analysis part, and solved any conflict in the quality assessment part, took part in the data extraction phase.

Zahraa Saker took part in the screening process, data extraction and quality assessment, wrote the abstract and introduction sections and edited the whole manuscript.

Fatma Haji took part in the screening process, data extraction and quality assessment, and wrote the method section.

Menna took part in the screening process, data extraction and quality assessment, wrote the result section, and drafted the tables.

Zeinab Khaled took part in the screening process, data extraction and quality assessment, and wrote the discussion section, strength and limitations, conclusion and list of abbreviation.

Mohamed Abd-ElGawad supervised the authors in all steps and performed peer-review.

All authors reviewed the final manuscript.

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Figures

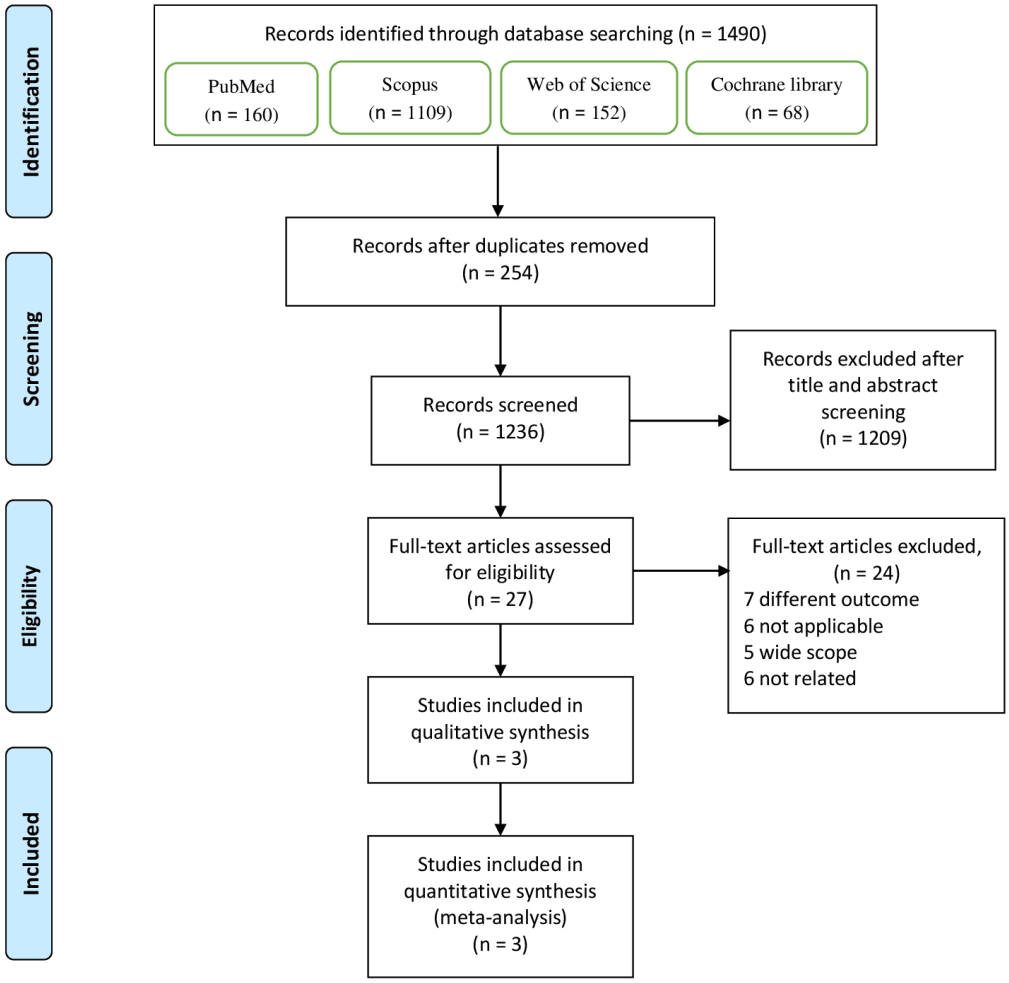

Figure 1

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

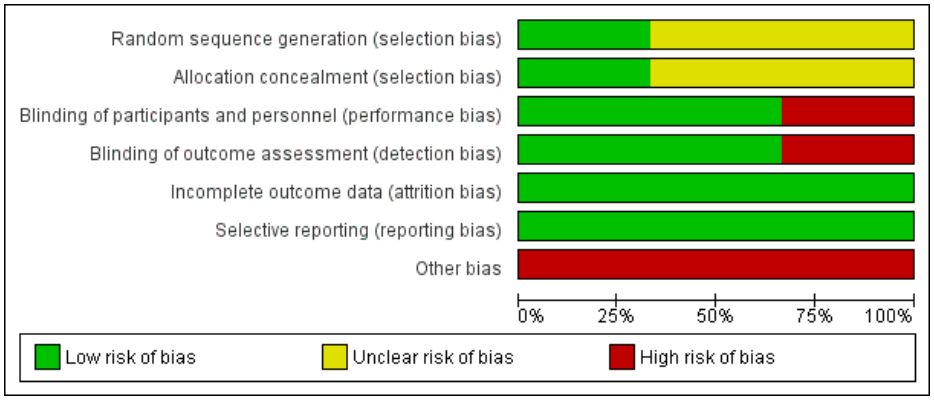

Figure 2

Risk of bias graph for randomized controlled trials using Excel tool to implement Rob2.

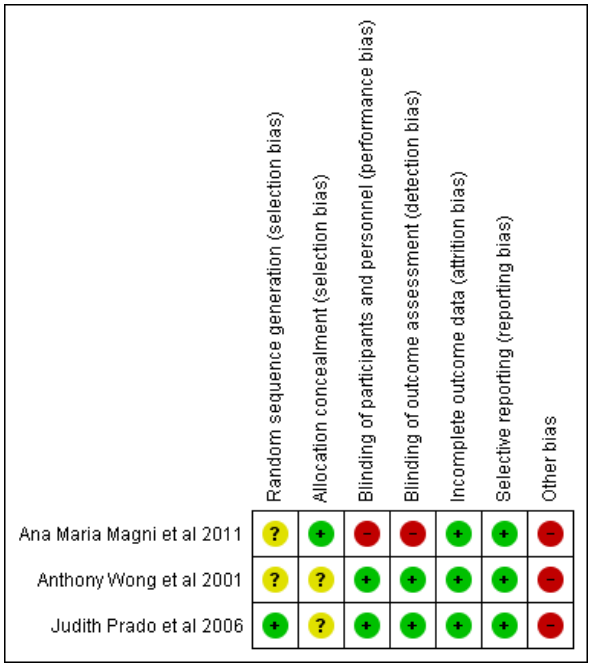

Figure 3

Risk of bias summary for randomized controlled trials using Excel tool to implement Rob2.

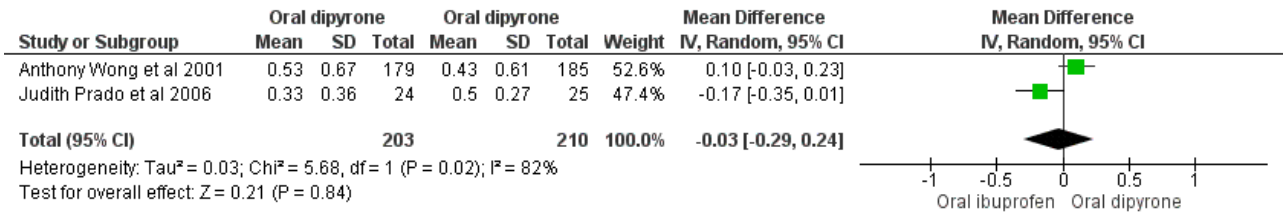

Figure 4

Decrease from baseline in temperature after 30min plot

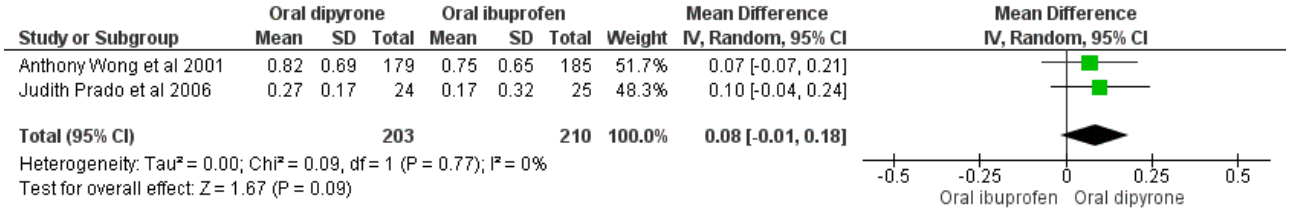

Figure 5

Decrease from baseline in temperature after 45 min plot

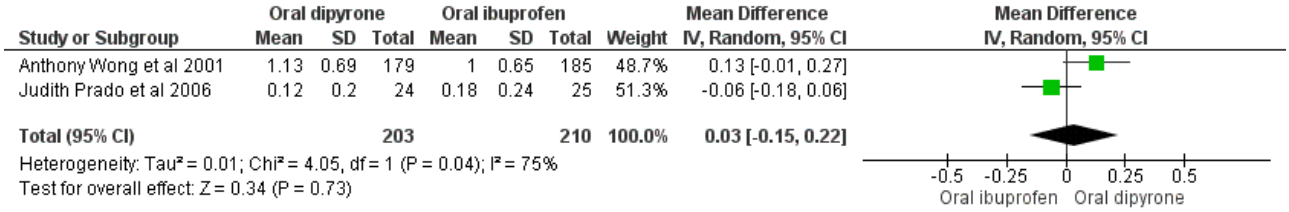

Figure 6

Decrease from baseline in temperature after 60 min plot

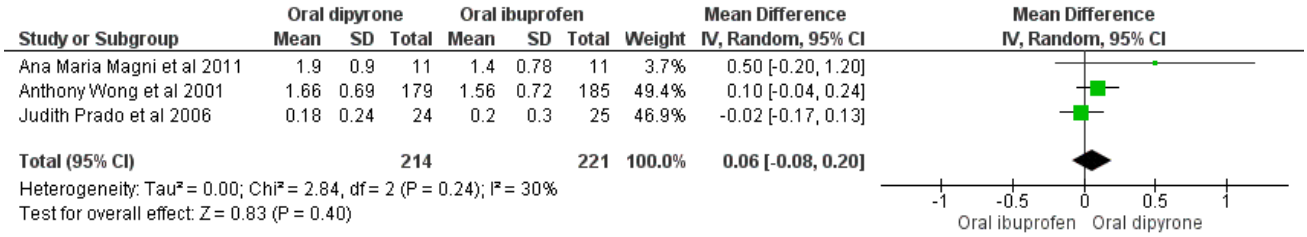

Figure 7

Decrease from baseline in temperature after 120 min plot

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- AntipyreticSupplementeryfile1.docx