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Antipyretic effect of oral dipyrone (Metamizole) compared to oral ibuprofen in febrile children: a systematic review and meta-analysis

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Abstract

Background Dipyrone (Metamizole) is a potent pain reliever and fever reducer with muscle relaxant properties, most commonly used as an analgesic and antipyretic agent. 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 children. In febrile children, 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 children. 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.

Keywords Antipyretic effect, Febrile Children, Oral dipyrone, Oral ibuprofen, Temperature

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Background

Fever is the most common issue in pediatric management. It requires careful consideration, being responsible for about a quarter of consultations in emergency and primary care departments [1–3]. It is often defined as a core temperature of 38 °C or higher with substantial differences among measurement sites including rectum, axillary, 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]. Including nonsteroidal anti-inflammatory drugs nonsteroidal anti-inflammatory drugs (NSAIDs) and paracetamol (acetaminophen), and metamizole [8, 9]. 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 pyrazalone derivative classified within the group of non-acidic, non-opioid medications 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 [10–12]. 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 [13]. However, it is still frequently used in practice guidelines for perioperative pain and fever management in many other countries in Europe, Australia, and Asia [14, 15].

Ibuprofen, which belongs to the NSAIDs, has been prescribed as an analgesic for acute and chronic pain and inflammatory conditions with a favorable overall safe profile [16, 17]. It was suggested for antipyretic use in febrile children by the American Academy of Pediatrics [18]. It shows a strong antipyretic effect with a long duration of temperature reduction; however, its administration must be monitored to avoid side effects [16].

In our study, we aim to review, summarize, and analyze these studies to understand the antipyretic profiles of oral dipyrone compared to oral ibuprofen in children.

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 [19, 20]. 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 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 [21].

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 min after drug administration. The baseline temperature was between 38.0 and 40.5℃. 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. A total of 254 records were eliminated due to duplicates. After title and abstract screening, 1209 records were excluded as irrelevant. The full texts of the remaining 27 records were assessed for eligibility. Of these, 24 records were further excluded because they did not compare the antipyretic effects of oral dipyrone with oral ibuprofen. Ultimately, this systematic review and meta-analysis included three randomized clinical trials. The PRISMA flowchart is shown in Fig. 1.

Characteristics of the included studies

A total of 547 febrile children were enrolled in the three included RCTs conducted in Brazil, Argentina, Chile, Mexico, and Peru. These RCTs were published between

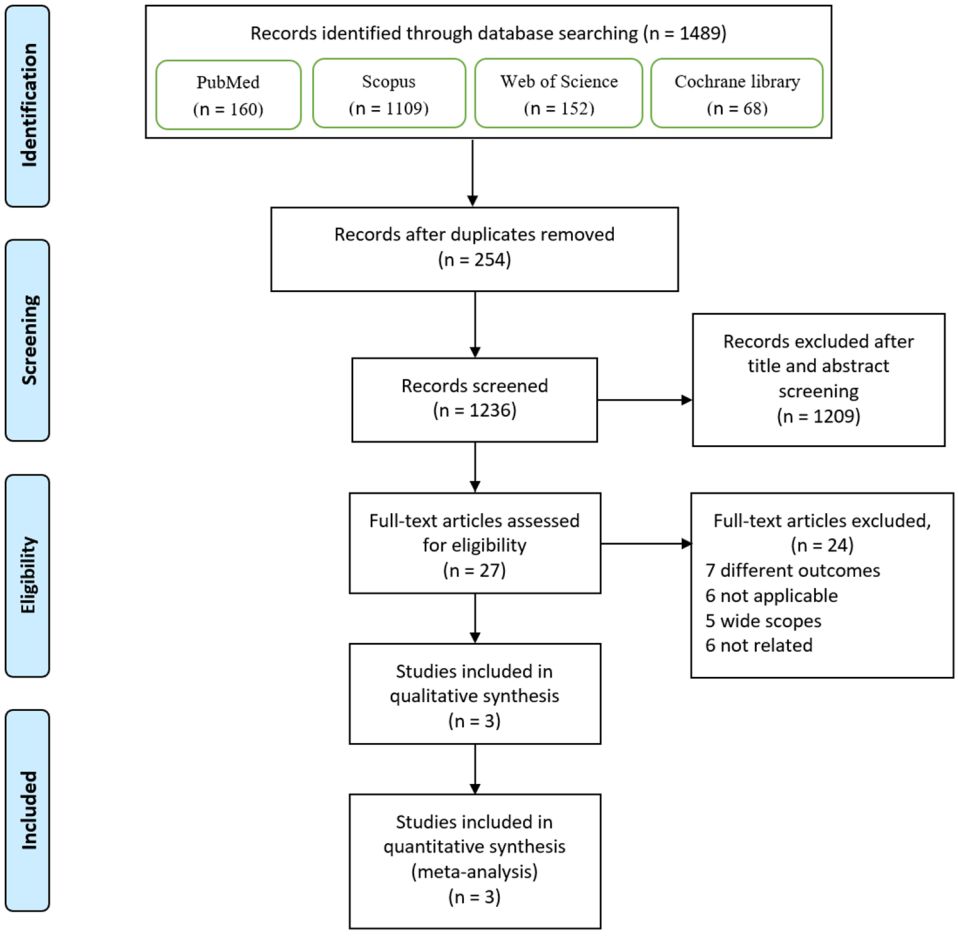

Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)

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

Study ID	Title	Study design, country, and timing	Criteria	Sample size	treatment regimen	Control group	study duration
Anthony Wong et al., 2001 [22]	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<39.20 C and 10 mg/kg for To.39.20 C.	8 months
Judith Prado et al., 2006 [23]	Antipyretic effifi-cacy 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 (15 mg/kg)	*N*= 25 Participants received single dose of oral ibuprofen (10 mg/kg)	5 months
Ana Maria Magni et al., 2011 [24]	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>=6 kg and <= 22 kg • fever at least for 4 h and up to 48 h	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 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(month) mean ± SD	Males (%)	Mean Baseline temperature	Weight (kg)	Race			
							White	Black	Asian	American Indian or Alaska Native
Anthony Wong et al., 2001 [22]	Oral dipyron 15 mg/kg	209	28 ± 18	128 (61.2%)	39.3 ± 0.6	13 ± 4	209 (100%)	0	0	0
	Oral ibuprofen 10 mg/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 15 mg/kg	24	16.3 ± 13.7	11 (45.8%)	38.8± 0.4	10.1± 2.4	24 (100%)	0	0	0
	Oral ibuprofen 10 mg/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 [24]	Oral dipyron 15 mg/kg	39	27 ± 20	21 (53.8%)	39.6 ± 0.4	-	39 (100%)	0	0	0
	Oral Ibuprofen 10 mg/kg	41	27 ± 20	23 (56.1%)	39.5 ± 0.3	-	41 (100%)	0	0	0

2001 and 2011. The median age ranged from 16.3 to 29 months, according to the available data. Without receiving concurrent treatments, 275 participants received oral ibuprofen, and 272 participants received oral dipyrone. The baseline temperature range was reported as 38 °C to 38.5 °C. The RCTs that were included have their demographic details compiled in Tables 1 and 2.

Quality assessment

The overall risk of bias in the included studies [22–24] was low. On the subject of the randomization process bias, two studies [22, 24] reported an inadequate randomization method and were judged as some concerns. Concerning the allocation concealment and randomization process, two studies [22, 23] were judged as some concerns due to the inadequate information about the allocation concealment and randomization. As regards to the blinding of participants and personnel, one study [24] was evaluated as high risk of bias as it was single-blinded study, whereas the other two studies [22, 23] were judged as low risk of bias due to sufficient blinding of the patients and examiners. Regarding the outcome assessment, one study [24] showed high risk of bias due to missing data over different time intervals, yet

the other two studies [22, 23] had a low risk of bias due to sufficient data. All the three studies [22–24] 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 [22–24]. 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. 4a). 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 (Fig. 4b and c). 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 [22, 23]. The results of the studies after 120 min of drug administration was also examined [22–24] 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. 4d). 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 seen 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 [24]. remarkably, other studies have reported similar frequencies of adverse events in the two groups [22, 23]. 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 [25]. 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 [26] shedding light on its safety profile. Ibuprofen is commonly used drug for also its analgesic and antipyretic efficacies over different age groups [27]. These two drugs had comparable safety profiles with regard to serious adverse effects, particularly gastrointestinal hemorrhage in overdose conditions and the risk of anaphylactic reactions. It is known that both drugs have the potential to induce anaphylactic reactions; in such cases, ibuprofen may worsen symptoms of pre-existing asthma, while metamizole can trigger bronchospasm [28–30].

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 [31–33] which contrasts with the outcomes

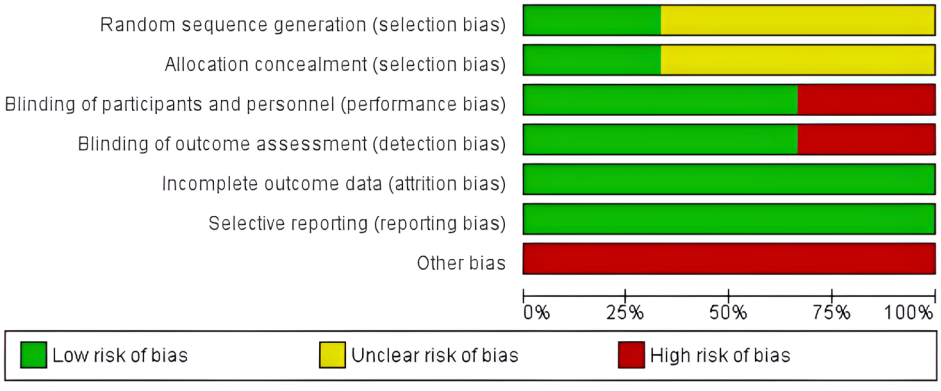

Fig. 2 Risk of bias graph for randomized controlled trials using Excel tool to implement Rob2

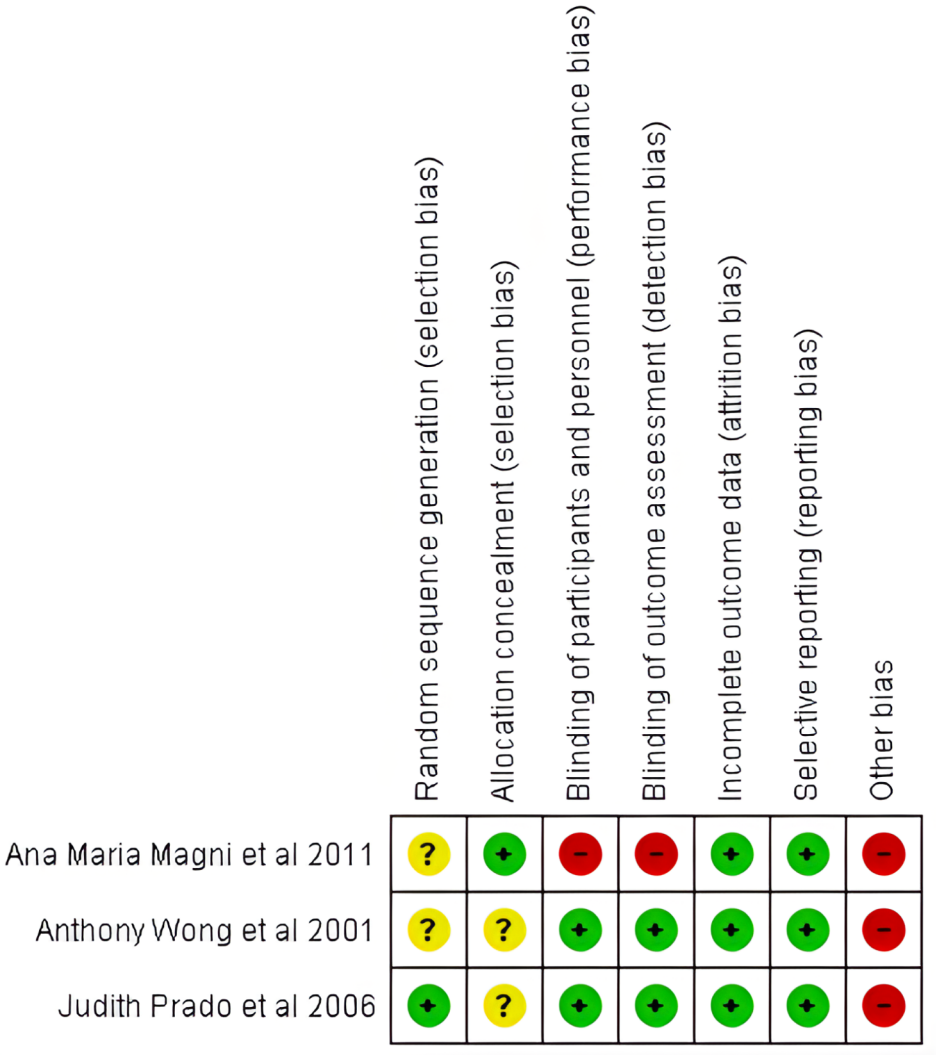

Fig. 3 Risk of bias summary for randomized controlled trials using Excel tool to implement Rob2

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 [33]. The peak of antipyretic activity is predicted to occur 2–4 h after delivery when the recommended doses are employed, such as 15 mg/kg for dipyrone and 10 mg/kg for ibuprofen [22–24]. Consequently, if no reduction in fever is observed within this time frame, it suggests a need to explore additional antipyretic options, despite both molecules having shown efficacy.

Ibuprofen and dipyrone were linked to the bulk of the unfavorable gastrointestinal side effects, which included nausea and diarrhea [22]. Weeping, anorexia, hypoactivity, shivering, and vomiting frequency were not different between the two groups, according to reports [23]. Without any evidence to back it up, dipyrone-related risks for aplastic anemia and agranulocytosis have already been widely characterized [34]. In addition, these reactions can occur even at standard doses 5 mg/kg/dose, underscoring the need for careful consideration and monitoring when prescribing dipyrone [35].

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

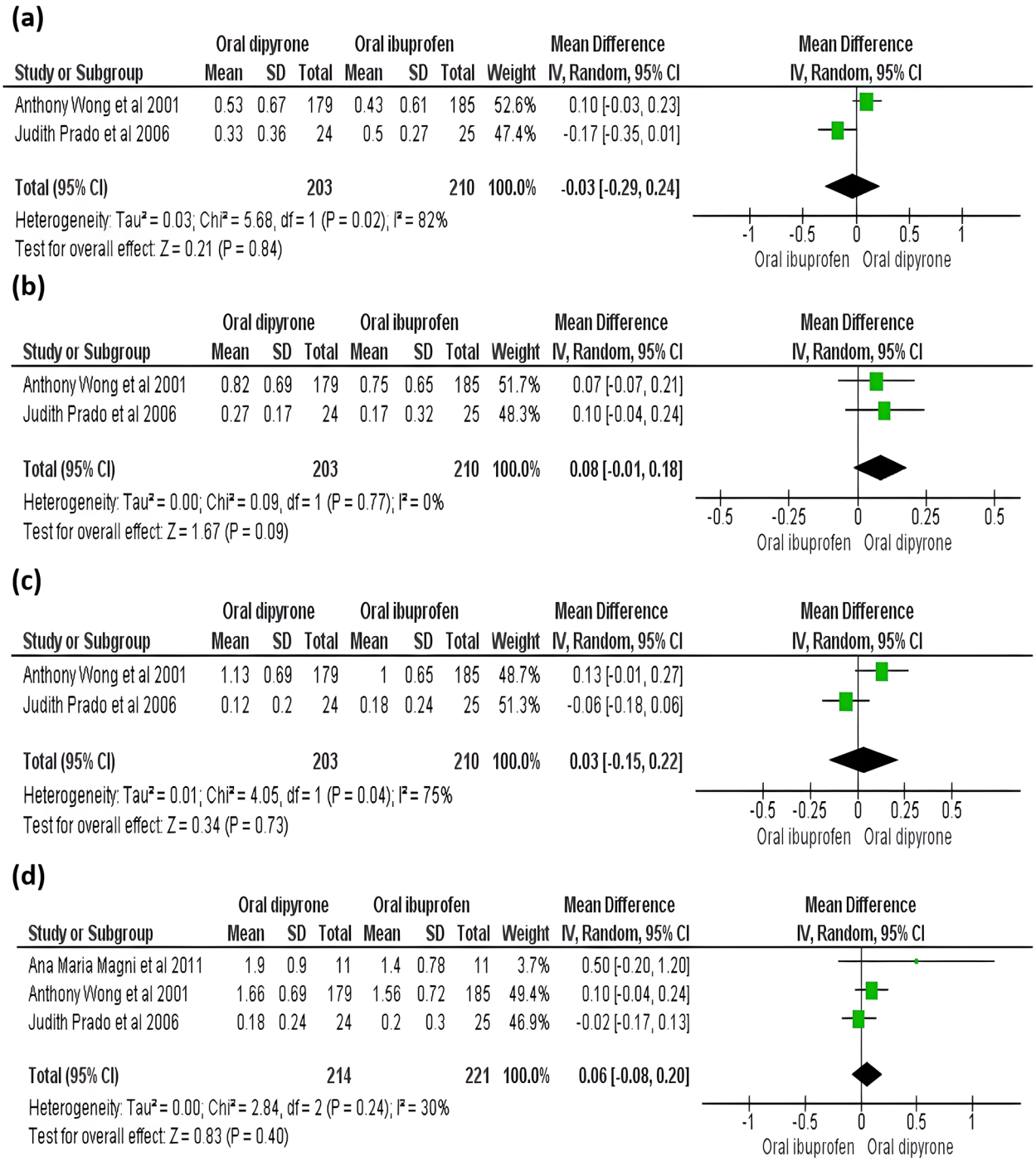

Fig. 4 **a**: Decrease from baseline in temperature after 30 min plot **b**: Decrease from baseline in temperature after 45 min plot **c**: Decrease from baseline in temperature after 60 min plot **d**: Decrease from baseline in temperature after 120 min plot

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 variation

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12887-024-05095-1.

Supplementary Material 1

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Not applicable.

Author 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.

Data availability
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.

Declarations

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.

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

Competing interests
The authors declare no competing interests.

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References

1. Whitburn S, Costelloe C, Montgomery AA, Redmond NM, Fletcher M, Peters TJ, et al. The frequency distribution of presenting symptoms in children aged six months to six years to primary care. Prim Health Care Res Dev. 2011;12(2):123–34.
2. de Bont EG, Lepot JM, Hendrix DA, Loonen N, Guldemond-Hecker Y, Dinant GJ, et al. Workload and management of childhood fever at general practice out-of-hours care: an observational cohort study. BMJ Open. 2015;5(5):e007365.
3. Sands R, Shanmugavadivel D, Stephenson T, Wood D. Medical problems presenting to paediatric emergency departments: 10 years on. Emerg Med J. 2012;29(5):379–82.
4. Taylor NA, Tipton MJ, Kenny GP. Considerations for the measurement of core, skin and mean body temperatures. J Therm Biol. 2014;46:72–101.
5. National Collaborating Centre for Ws, Children's H. National Institute for Health and Care Excellence. Guidelines. Feverish Illness in Children: Assessment and Initial Management in Children Younger Than 5 Years. London: Royal College of Obstetricians and Gynaecologists (UK) Copyright © 2013 National Collaborating Centre for Women's and Children's Health.; 2013.
6. Barbi E, Marzuillo P, Neri E, Naviglio S, Krauss BS. Fever in children: pearls and pitfalls. Child (Basel). 2017;4(9).
7. Aronoff DM, Neilson EG. Antipyretics: mechanisms of action and clinical use in fever suppression. Am J Med. 2001;111(4):304–15.
8. Bárzaga Arencibia Z, Choonara I. Balancing the risks and benefits of the use of over-the-counter pain medications in children. Drug Saf. 2012;35(12):1119–25.
9. Andrade S, Bartels DB, Lange R, Sandford L, Gurwitz J. Safety of metamizole: a systematic review of the literature. J Clin Pharm Ther. 2016;41(5):459–77.
10. Witschi L, Reist L, Stammschulte T, Erlenwein J, Becke K, Stamer U. [Perioperative use of metamizole and other nonopioid analgesics in children: results of a survey]. Anaesthesist. 2019;68(3):152–60.
11. Blaser LS, Tramonti A, Egger P, Haschke M, Krähenbühl S, Rätz Bravo AE. Hematological safety of metamizole: retrospective analysis of WHO and Swiss spontaneous safety reports. Eur J Clin Pharmacol. 2015;71(2):209–17.
12. Vizdiklar C, Akici N, Aydin V, Donertas B, Alkan A, Akici A. Evaluation of injectable metamizole utilization in children and adults in primary care. Int J Clin Pharmacol Ther. 2020;58(12):718–26.
13. Hedenmalm K, Spigset O. Agranulocytosis and other blood dyscrasias associated with dipyrone (metamizole). Eur J Clin Pharmacol. 2002;58(4):265–74.
14. Zahn J, Eberl S, Rödle W, Rascher W, Neubert A, Toni I. Metamizole Use in Children: analysis of drug utilisation and adverse drug reactions at a German University Hospital between 2015 and 2020. Paediatr Drugs. 2022;24(1):45–56.
15. Messerer B, Grögl G, Stromer W, Jaksch W. [Pediatric perioperative systemic pain therapy: Austrian interdisciplinary recommendations on pediatric perioperative pain management]. Schmerz. 2014;28(1):43–64.
16. Lesko SM, Mitchell AA. An assessment of the safety of pediatric ibuprofen. A practitioner-based randomized clinical trial. JAMA. 1995;273(12):929–33.
17. Rainsford KD. Ibuprofen: pharmacology, efficacy and safety. Inflammopharmacology. 2009;17(6):275–342.
18. Paul IM, Walson PD. Acetaminophen and ibuprofen in the treatment of pediatric fever: a narrative review. Curr Med Res Opin. 2021;37(8):1363–75.
19. Higgins J, Green S. Cochrane Handbook for Systematic Reviews of Interventions2009.
20. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009;339:b2535.
21. Higgins JPT, Altman DG. Assessing Risk of Bias in Included Studies. Cochrane Handbook for Systematic Reviews of Interventions2008. pp. 187–241.
22. Wong A, Sibbald A, Ferrero F, Plager M, Santolaya ME, Escobar AM et al. Antipyretic effects of Dipyrone Versus Ibuprofen Versus Acetaminophen in Children: results of a multinational, randomized, modified double-blind study. Clin Pediatr (Phila). 2001;40(6):313–24.
23. Prado J, Daza R, Chumbes O, Loayza I, Huicho L. Antipyretic efficacy and tolerability of oral ibuprofen, oral dipyrone and intramuscular dipyrone in children: a randomized controlled trial. Sao Paulo Med J = Revista paulista de Med. 2006;124(3):135–40.
24. Magni AM, Scheffer DK, Bruniera P. Antipyretic effect of ibuprofen and dipyrone in febrile children. Jornal De Pediatria. 2011;87(1):36–42.
25. Dinarello CA. Infection, fever, and exogenous and endogenous pyrogens: some concepts have changed. J Endotoxin Res. 2004;10(4):201–22.
26. Malvar Ddo C, Soares DM, Fabricio AS, Kanashiro A, Machado RR, Figueiredo MJ, et al. The antipyretic effect of dipyrone is unrelated to inhibition of PGE(2) synthesis in the hypothalamus. Br J Pharmacol. 2011;162(6):1401–9.
27. Stessel B, Boon M, Pelckmans C, Joosten EA, Ory JP, Wyckmans W, et al. Metamizole vs. ibuprofen at home after day case surgery: a double-blind randomised controlled noninferiority trial. Eur J Anaesthesiol. 2019;36(5):351–9.

28. Wertli MM, Flury JS, Streit S, Limacher A, Schuler V, Ferrante AN, et al. Efficacy of metamizole versus ibuprofen and a short educational intervention versus standard care in acute and subacute low back pain: a study protocol of a randomised, multicentre, factorial trial (EMISI trial). BMJ Open. 2021;11(10):e048531.
29. Baxter L, Cobo MM, Bhatt A, Slater R, Sanni O, Shinde N. The association between ibuprofen administration in children and the risk of developing or exacerbating asthma: a systematic review and meta-analysis. BMC Pulm Med. 2024;24(1):412.
30. Miljkovic M, Rancic N, Simić R, Stamenkovic D, Dragojevic Simic V, Metamizole. Current status of the safety and efficacy. Hosp Pharmacol - Int Multidisciplinary J. 2018;5:694–704.
31. Vera P, Zapata L, Gich I, Mancebo J, Betbese AJ. [Hemodynamic and antipyretic effects of Paracetamol, metamizol and dexketoprofen in critical patients]. Med Intensiva. 2012;36(9):619–25.
32. Ianosi B, Rass V, Gaasch M, Huber L, Lindner A, Hackl WO, et al. An observational study on the use of intravenous non-opioid analgesics and Antipyretics in Poor-Grade Subarachnoid Hemorrhage: effects on Hemodynamics and systemic and Brain temperature. Ther Hypothermia Temp Manag. 2020;10(1):27–36.
33. Gozzoli V, Treggiari MM, Kleger GR, Roux-Lombard P, Fathi M, Pichard C, et al. Randomized trial of the effect of antipyresis by metamizol, propacetamol or external cooling on metabolism, hemodynamics and inflammatory response. Intensive Care Med. 2004;30(3):401–7.
34. Schönhöfer P, Offerhaus L, Herxheimer A. Dipyrone and agranulocytosis: what is the risk? Lancet. 2003;361(9361):968–9.
35. Hoffmann F, Bantel C, Jobski K. Agranulocytosis attributed to metamizole: an analysis of spontaneous reports in EudraVigilance 1985–2017. Basic Clin Pharmacol Toxicol. 2020;126(2):116–25.

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