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Comparison of Effectivenness Between Ibuprofen and Paracetamol in the Treatment of Fever in Children Aged 0-18 Years a Systematic Review and Meta-Analysis of Randomized Control Trials

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ABSTRACT

Fever is defined as one of the acute adaptive physiological responses to conditions caused by infection, characterized by an increase in body temperature ≥38°C. Acetaminophen (paracetamol) and ibuprofen are the only two choices of over-the-counter drugs for the antipyretic class. Acetaminophen (paracetamol) and ibuprofen are the two over-the-counter drug choices, the only antipyretic class most often prescribed to treat fever in children. Acetaminophen (paracetamol) is considered the safest over-the-counter drug to control fever in children, while ibuprofen is a non-steroidal anti-inflammatory drug that works by inhibiting the synthesis of prostaglandin E2 in the anterior hypothalamus thereby reducing the temperature regulation center and can achieve a cooling effect. This made the authors interested in presenting a systematic review to compare the antipyretic profiles of acetaminophen with ibuprofen in the treatment of fever in children aged 0-18 years. Articles were searched through the database from January 2019 - January 2022. Searches were obtained from the PUBMED database. There was no attempt by the authors to specifically search for unpublished articles in English or Indonesian. Free full text or articles that can be downloaded for free (open access) articles with randomized controlled trials. The subjects used were children aged 0-18 years. Based on research results that ibuprofen is more effective than acetaminophen in treating fever in children. This was evidenced from the 8 articles discussed, 4 of which said that the use of ibuprofen was more effective in lowering body temperature, while 3 articles concluded that both were balanced and equally effective, while 1 other said that combination or alternating therapy resulted in more effectiveness than monotherapy in lowering body temperature. body temperature. However, the benefits appear to be small in comparison and may not be clinically relevant.

Keywords: *Fever, Ibuprofen, Paracetamol*

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INTRODUCTION

Fever is defined as one of the acute adaptive physiological responses to conditions caused by infection, characterized by an increase in body temperature ≥38°C (G. Chen dkk., 2020). Fever is the main clinical symptom of some children (Alaje et al., 2020) after pyrogen infection that can heal on its own (Guan dkk., 2020), starting with an increase in body temperature from the normal/regulatory point and then increasing the body's cardiopulmonary burden, thus worsening the prognosis of the child's health condition, especially children with a history of congenital diseases.

The prevalence of fever in children aged less than 5 years in Nigeria is ±35% (Alaje et al., 2020), ±30% in the US from 2014 and 2017, and 27% in Turkey (Oncel et al., 2021).

Acetaminophen (paracetamol) and ibuprofen are the two most commonly prescribed over-the-counter antipyretics for fever in children (Wang dkk., 2020). Paracetamol is indicated from birth, while ibuprofen is indicated starting from three months of age (J. Chen dkk., 2020). Acetaminophen (paracetamol) is considered the safest over-the-counter drug to control fever in children while ibuprofen is a non-steroidal anti-inflammatory type drug that works by inhibiting prostaglandin E2 synthesis in the anterior hypothalamus, thereby reducing the temperature regulation center and can achieve a cooling effect (Garg dkk., 2020). In addition, ibuprofen also inhibits the production of tumor necrosis factor by stimulating the body to produce endogenous cryogen so that it has anti-inflammatory and cooling effects on body temperature.

Treatment of fever is often over-treated due to "fever phobia" (Doria et al., 2021). The results of several epidemiological studies show that there is a significant relationship between the overuse of paracetamol and the incidence of asthma related to two factors, namely dose and response (Rinott dkk., 2020). Inhibition of the COX pathway can also activate the lipoxygenase pathway, causing increased leukotriene synthesis, and resulting in bronchospasm and asthma exacerbation (Sherbash et al., 2020). Empirical evidence accumulated over ±30 years that paracetamol pills has an exacerbation of asthma that some doctors in the world do not recommend to be given so that what stands out from the data extraction is ibuprofen.

Acetaminophen and ibuprofen were shown to be effective in controlling fever at 60 minutes but the efficacy of ibuprofen was stronger in the first minute than paracetamol. The treatment efficacy between acetaminophen and ibuprofen can be seen with the example of ARI cases in children, where 1000 mg IV paracetamol is equal to 400 mg IV ibuprofen in reducing fever. However, the public demand for paracetamol is twice as high as for ibuprofen (Ashina dkk., 2021). Due to several epidemiologic studies in North America, the United Kingdom, and Europe that suggest ibuprofen may play a role in the development of serious bacterial infections, some authors also warn against the use of ibuprofen in younger infants, citing a higher risk of acute kidney injury, particularly in the context of dehydration (De Santiago-Martín dkk., 2020). For

this reason, it is necessary to recognize the side effects of the two drugs. The side effects of using paracetamol and ibuprofen are also not small according to (Barbagallo & Sacerdote, 2018), the side effects of using paracetamol include nausea, diarrhea, and itchy rashes while the side effects of using ibuprofen consist of nausea, vomiting, and abdominal pain.

The purpose of writing several systematic reviews is to compare the antipyretic profile of acetaminophen with ibuprofen in the treatment of fever in children aged 0-18 years (Black dkk., 2019). It will also discuss the efficacy and safety of the combination or alternate administration of acetaminophen and paracetamol using PRISMA guidelines.

RESEARCH METHODOLOGY

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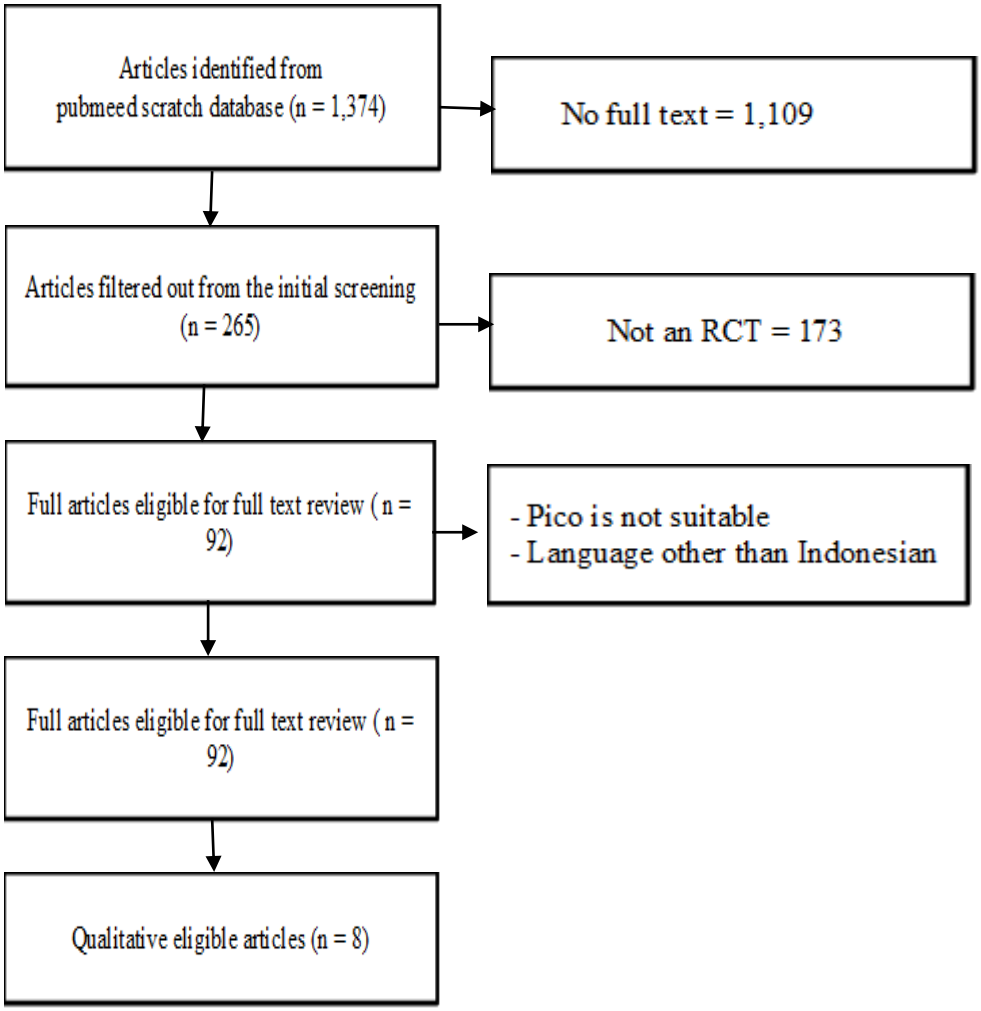
Acetaminophen and ibuprofen were shown to be effective in controlling fever at 60 minutes but the efficacy of ibuprofen was stronger in the first minute than paracetamol. The treatment efficacy between acetaminophen and ibuprofen can be seen with the example of ARI cases in children, where 1000 mg IV paracetamol is equal to 400 mg IV ibuprofen in reducing fever. However, the public demand for paracetamol is twice as high as for ibuprofen (Jain dkk., 2019). Due to several epidemiologic studies in North America, the United Kingdom, and Europe that suggest ibuprofen may play a role in the development of serious bacterial infections, some authors also warn against the use of ibuprofen in younger infants, citing a higher risk of acute kidney injury, particularly in the context of dehydration (Bilal dkk., 2019). For this reason, it is necessary to recognize the side effects of the two drugs. The side effects of using paracetamol and ibuprofen are also not small according to (Klok dkk., 2020), the side effects of using paracetamol include nausea, diarrhea, and itchy rashes while the side effects of using ibuprofen consist of nausea, vomiting, and abdominal pain.

The purpose of writing several systematic reviews is to compare the antipyretic profile of acetaminophen with ibuprofen in the treatment of fever in children aged 0-18 years. It will also discuss the efficacy and safety of the combination or alternate administration of acetaminophen and paracetamol using PRISMA guidelines.

RESULT AND DISCUSSION



PRISMA flow diagram for article selection in a systematic review

Table 1 Critical assessment

Criteria	(Alaje et al., 2020)	(Tan, Braithwaite, Mckinlay, et al., 2020)	(Oncel et al., 2021)	(Doria et al., 2021)	(Sherbash et al., 2020)	(Tan, Braithwaite, McKinlay, et al., 2020)	(Trippella et al., 2019)	(Yin et al., 2022)
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
Does the experiment clearly answer the clinical question?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Ya
Was the delivery of the intervention to participants randomized?	Yes	Combinatio n	Yes	Not explained	Yes	Yes	Yes	Ya

Criteria	(Alaje et al., 2020)	(Tan, Braithwaite, Mckinlay, et al., 2020)	(Oncel et al., 2021)	(Doria et al., 2021)	(Sherbash et al., 2020)	(Tan, Braithwaite, McKinlay, et al., 2020)	(Trippella et al., 2019)	(Yin et al., 2022)
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
Were all patients included in the study accounted for in the conclusions and analysis?	No	No	No	Not explained	No	No	No	Tidak
Were patients, health workers, and additional investigators blinding?	Single blind	No	Yes	Not explained	No	Yes	No	Tidak
Were the study groups similar at the start of the study?	Yes	Yes	Yes	Yes	Yes	No	Yes	Ya
Outside of the intervention being studied, were the study groups treated equally?	Yes	Yes	Yes	Yes	Yes	explained	Yes	Ya
Was the effect of the intervention large enough?	Yes significant	Yes	Yes	Not explained	Not explained	Yes	No	Ya signifikan
What is the precision of the estimate of the intervention effect?	5% and 80% power	SMD, OR, CI 95%	95% CI	Not explained	OR	Not explained	MD, RR, 95% CI	MD, RR, CI 95%
Do the benefits provided by the intervention outweigh the harms and costs?	Not explained	Not explained	Not explained	Not explained	Not explained	OR, 95% CI	Not explained	Tidak dijelaskan
Are the results applicable to the practice context or local population?	Yes	Yes	Yes	Yes	Yes	Not explained	No	Ya

Criteria	(Alaje et al., 2020)	(Tan, Braithwaite, Mckinlay, et al., 2020)	(Oncel et al., 2021)	(Doria et al., 2021)	(Sherbash et al., 2020)	(Tan, Braithwaite, McKinlay, et al., 2020)	(Trippella et al., 2019)	(Yin et al., 2022)
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
Are all other clinically important outcomes considered in this article?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Ya

Table 2 Summary of Study Results

No	Study	Subject	Local	Results
1	(Alaje et al., 2020)	140 eligible children aged 6.59 months with a temperature of 38℃-40℃	University of calabar teaching hospitan in negria	After initial drug administration, most children in the ibuprofen group had their temperature reduced to a normal level of 37.6℃ compared to those in the paracetamol group. The difference in the proportion of febrile children between these groups was statistically significant at three time points: 15 hours (p=0, 04), 2 hours (p=0, 03) and 2.5 hours (0, 01) at the end of the first hour two children in the ibuprofen group (2, 9%) were observed to have no fever while those in the paracetamol group began to have no fever in favor of ibuprofen as a more potent antiperatic with effect size values ranging from 0.19 to 0.33.
2	(Tan, Braithwaite, Mckinlay, et al., 2020)	Children under 2 years old	Systematic searches of MEDLINE, Embase, CINAHL, and Cochrane Central Register of Controlled Trials databases and ClinicalTrials.gov trial registry and Australian New Zealand Clinical Trials Registry	In this study, ibuprofen use was associated with reduced temperature and less pain in the first 24 hours compared to acetaminophen use. The lack of analgesic outcome data within 4 hours of use weakens the clinical importance of these findings. Both drugs appear to have similar safety profiles in the short term, with very low rates of adverse effects overall. Evidence regarding the risk of serious bacterial infections remains inconclusive, and there are limited data on younger infants and long-term side effects. Large randomized trials are needed to address these knowledge gaps, designed to include and report on subgroups of infants younger than 6 months and to investigate the safety of acetaminophen and ibuprofen as primary endpoints, with long-term follow-up and monitoring for adverse effects.
3	(Oncel et al., 2021)	Patients between 18 and 65 years old, who have a body temperature of more than 38°C	ER at Pamukkale University	Although both drugs were shown to be effective in controlling fever by the 60th minute, ibuprofen's stronger efficacy in the first minute may allow for rapid discharge of patients from the emergency department

No	Study	Subject	Local	Results
4	(Doria et al., 2021)	Pediatric patients with acute mild-moderate fever and pain in the hospital	Italy	Precision medicine, patient profiles may benefit differently from paracetamol or ibuprofen according to the different efficacy and safety features of the two drugs
5	(Sherbash et al., 2020)	All databases were searched from baseline to September 2017	PubMed, Science Citation Index, Embase, Cochrane library, and Clinical Trials.gov.	No difference in the likelihood of developing asthma or showing asthma exacerbation in children receiving paracetamol compared with ibuprofen
6	(Tan, Braithwaite, McKinlay, et al., 2020)	Infants born at 32 weeks gestation	Two regions of New Zealand: Auckland and Wellington	In children with asthma, two previous studies have compared the effects of paracetamol and ibuprofen use on asthma symptoms. Lesko et al, in a post hoc analysis of short-term paracetamol or ibuprofen use for febrile illness, reported a two-fold higher risk of unscheduled outpatient visits for asthma in the paracetamol group. In contrast, Sheehan et al reported that among young children (aged 12-59 months) with mild persistent 'asthma', necessary paracetamol use was not associated with a higher incidence of asthma.
7	(Trippella et al., 2019)	Database as of September 2018	MEDLINE and EMBASE databases	According to the results of our recent review, combination or alternating therapy resulted more effective than monotherapy in lowering body temperature. However, the benefits appear smaller than those reported in the previous 2013 Cochrane review and may not be clinically relevant. Similar results were observed by pooling data from two studies that evaluated the effect on child discomfort and the number of drug doses. To date, the evidence is insufficient to encourage the combination or alternative of paracetamol and ibuprofen over monotherapy for treating febrile children.
8	(Yin et al., 2022)	Mean age ranged from 2 to 8 years. All studies included body temperature after treatment. All these studies were published from 2012 to 2018. Sample sizes ranged from 80	Systematic searches through Medline/PubMed, EMBASE, Cochrane Library, and China National Knowledge Infrastructure databases.	Studies show that ibuprofen is more effective than acetaminophen in children with infectious fever

No	Study	Subject	Local	Results
		to 522. The study included 1,773 patients with infectious fever, 822 with ibuprofen, and 891 with paracetamol.		

Comparison of the Effectiveness of Using Ibuprofen and Paracetamol in the Treatment of Fever in Children 0-18 Years of Age

Based on the results of research that ibuprofen is more effective than acetaminophen in treating fever in children. This is evidenced by 8 articles that discuss, 4 of them:

In (Middeldorp dkk., 2020), proving that after initial drug administration, most children in the ibuprofen group experienced a decrease in temperature to a normal level of 37.6oC compared to the paracetamol group (Rubin dkk., 2020). The difference in the proportion of febrile children between these groups was statistically significant at three time points: 15 hours (p=0.04), 2 hours (p=0.03) and 2.5 hours (0.01) at the end of the first hour two children in the ibuprofen group (2, 9%) were observed to have no fever while those in the paracetamol group began to have no fever in favor of ibuprofen as the more potent antiperatic with effect size values ranging from 0.19 to 0.33.

In the study (Dobson & Giovannoni, 2019), ibuprofen use was associated with decreased temperature and less pain in the first 24 hours compared to acetaminophen use. The lack of analgesic outcome data within 4 hours of use weakens the clinical importance of these findings (Critchley dkk., 2020). Both drugs appear to have similar safety profiles in the short term, with very low rates of adverse effects overall (Lumley dkk., 2021). Evidence regarding the risk of serious bacterial infections remains inconclusive, and there are limited data on younger infants and long-term side effects (Turner dkk., 2019). Large randomized trials are needed to address these knowledge gaps, designed to include and report on subgroups of infants younger than 6 months and to investigate the safety of acetaminophen and ibuprofen as primary endpoints, with long-term follow-up and monitoring for adverse effects.

Meanwhile according to although both drugs were shown to be effective in controlling fever by the 60th minute (Yustikasari dkk., 2021), the stronger efficacy of ibuprofen in the first minute may allow for rapid discharge of patients from the emergency department.

Whereas in (Hajek dkk., 2019), the study showed that ibuprofen was more effective than acetaminophen in children with infectious fever.

In addition to the article that mentions that the use of ibuprofen is more effective than paracetamol in reducing fever, 3 other articles show that both are equally effective depending on certain assessments, including:

According to (Karavani dkk., 2019), Precision medicine, patient profiles may benefit differently from paracetamol or ibuprofen according to the different efficacy and safety features of the two drugs.

While according to (Powles dkk., 2020), There was no difference in the likelihood of developing asthma or showing asthma exacerbation in children receiving paracetamol compared to ibuprofen.

Meanwhile, according to (Murthy dkk., 2020), In children with asthma, two previous studies have compared the effects of using paracetamol and ibuprofen on asthma symptoms. Lesko et al, in a post hoc analysis of short-term paracetamol or ibuprofen use for febrile illness, reported a two-fold higher risk of unscheduled outpatient visits for asthma in the paracetamol group (Gnocchi dkk., 2022). In contrast, Sheehan et al reported that among young children (aged 12-59 months) with mild persistent 'asthma', necessary paracetamol use was not associated with a higher incidence of asthma.

Different results were shown by (Manson dkk., 2019), According to the results of our recent review (Wisnu dkk., 2021), combination or alternating therapy resulted more effective than monotherapy in lowering body temperature. However (Shah dkk., 2019), the benefits appear smaller than those reported in the previous 2013 Cochrane review and may not be clinically relevant (Rodriguez-Wallberg dkk., 2023). Similar results were observed by pooling data from two studies that evaluated the effect on child discomfort and the number of drug doses (Shibeshi dkk., 2021). To date, the evidence is insufficient to encourage combinations or alternatives to paracetamol and ibuprofen over monotherapy for treating febrile children.

CONCLUSION

Based on the results of the study that ibuprofen is more effective than acetaminophen in treating fever in children. It was proven from 8 articles that discussed, 4 of them said that the use of ibuprofen was more effective in lowering body temperature, while 3 articles concluded that the two were balanced and equally effective, while 1 other said that combination or alternating therapy resulted more effective than monotherapy in lowering body temperature. However, the benefits appear smaller than and may not be clinically relevant.

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