# RESEARCH ARTICLE



# Intravenous and Oral Paracetamol Have the Same Effect in Reducing Fever in Pediatric Patients

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**Background:** The antipyretic effect of intravenous versus oral paracetamol is not well known. This study was aimed to compare the antipyretic effect of intravenous and oral paracetamol therapy to reduce fever.

Materials and Methods: This was an open-label randomized clinical trial study. The subjects were children who presented to Pediatric Ward and Emergency of Haji Adam Malik Hospital, aged from 2 months to 18 years old, with axillary temperature ≥38.0°C. Subjects were divided into two groups, group 1 received 15 mg/kg paracetamol intravenous and group 2 received the same dose of paracetamol but given through intravenous. The temperature reduction was analyzed by ANOVA, and the change in temperature was recorded at 0, 15, 30, 60, 120, and 180 minutes after drug administration.

**Results:** In the first group, the mean temperature was decreased (p<0.001) from 15 to 180 minutes after the administration of paracetamol. Nausea was documented as the adverse effect for both oral and intravenous administration groups.

**Conclusion:** The administration of 15 mg/kg paracetamol, either though intravenous or oral, have similar effect in reducing fever in children. Paracetamol therapy though intravenous route can be given if it cannot be given orally.

**Keywords:** antipyretic, pediatrics, fever, intravenous, oral, paracetamol

#### Introduction

Fever is a common symptom found in children, and is considered as the most common cause of medical treatment seeking. Fever management for children utilizes different approaches.¹ It is not a disease, but a physiological mechanism functioning to fight infection.² Fever is defined as rectal temperature of ≥38.0°C.³ Healthcare personnel are responsible for providing education of the correct use of antipyretics to parents.⁴

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Paracetamol or acetaminophen is two recognized names for one chemical compound deriving from N-acetyl-para-aminophenol which has antipyretic and analgesic effects.<sup>5</sup> Current guidelines recommend that antypiretics be administrated to children with fever otherwise appear healthy in effort to provide comfort rather than used to lower the body temperature.<sup>2,6</sup> Paracetamol is the safest and most frequently used antipyretics in children and is the first choice of medicine to overcome fever. It is safe in





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its standard dose (10-15 mg/kg) by either rectal, oral, or intravenous administration.<sup>5,7</sup> The elimination half-life of oral paracetamol varies between 20-89 minutes, while the intravenous paracetamol is around 2.7 hours.<sup>8</sup>

Some researches stated that intravenous paracetamol is better than oral paracetamol<sup>9,10</sup>, however some contras were also found. Therefore, this study was done to compare the antipyretic efficacy between intravenous and oral paracetamol with standard dose of 15 mg/kg, and to evaluate its adverse effects such as nausea, vomiting, and erythema or urticaria.<sup>3,11</sup>

# Materials and methods

This study was conducted between November 2018 and February 2019, in Pediatric Emergency and Ward at H. Adam Malik Hospital. This was an open-label randomized clinical trial, which compared the efficacy between intravenous and oral paracetamol in pediatric patients with fever. This study had been approved by Ethical Committee of Health Research from Faculty of Medicines with ethical number 142/Date/KEPK FK USU-RSUP HAM/2018, Universitas Sumatera Utara/H. Adam Malik Hospital, Medan.

### Subject Collection

The subject in this study were fever inpatient whose age from 2 month to 18 years old, and whose axilary temperature ≥38.0°C. Subjects with history of icterus and liver dysfunction were excluded.

# Subjects Treatment

Subjects were divided into two groups. The first group was consist of pediatric patients treated with intravenous paracetamol for 15 minutes, with composition of 1000 mg paracetamol in 100 mL solution, using infusion solution of Paracetamol from Mersi, PT Darya-Varia (Jakarta, Infonesia). And the second group was consist of pediatric patients treated with oral paracetamol, with composition of 120 mg in 5 mL solution in form of syrup, from Kimia Farma (Jakarta, Indonesia) with dose 15 mg/kg. Axillary temperatures were measured by a digital thermometer with MC-245 Model (Omron, Osaka, Japan) before and after paracetamol administration. If the temperature was measured as ≥38°C, paracetamol was administered to the patients accordingly. The outcome was the presence of fever among both groups after paracetamol administration.

The observation of temperature reduction made in intravenous and oral administration of paracetamol was

done at minute 0, 15, 30, 60, 120 and 180. While the observed adverse effects such as nausea, vomiting, and erythema.

# Statistical Analysis

Data were analyzed using the "intention to treat" approach, in which all subjects that meet inclusion and exclusion criteria in the beginning of the research were analyzed. The data were processed and analyzed with Statistical Package for Social Sciences for Windows (SPSS), at confidence interval (CI) 95%, and significance level p<0.05. Chisquare test was done to observe the different effects of paracetamol administration in both groups on fever and non fever. Unpaired T-test was done to determine the difference in temperature dropping of both groups. ANOVA test was done to find out the temperature difference both groups at six different measurement time.

## Results

Between November 2018 to February 2019, there were 206 subjects participating in this study; 103 subjects were administered with 15 mg/kg of intravenous paracetamol (group 1), and the other 103 subjects were administered with 15 mg/kg of oral paracetamol (group 2). Demographic characteristics of the two groups are shown in Table 1. Both groups showed similar characteristics, there were no significant differences between both groups regarding sex, age, diagnosis, height, body weight, nutritional status, and baseline temperature.

In Table 2, both groups were compared after grouping the subjects based on subjects with fever and no fever. There were no significant correlation of subjects with fever and without fever with either intravenous or oral paracetamol, even after the observation times (p>0.05).

The average temperature of group 2 was decreased faster after 15 minutes after the paracetamol administration, while the average temperature of group 1 temperature showed a more stable decrease. Even with different patterns, both intravenous and oral paracetemol end up with similar average body temperature after 180 minutes after the administration (±37.1°C). The administration of paracetamol through intravenous showed more stable temperature decreased compared to oral paracetamol (Figure 1).

Differences in temperature reduction of both groups are illustrated in Table 3. In the first group, after paracetamol

Table 1. Demographics and baseline characteristics of subjects.

	Paracetamol A			
Characteristics	Intravenous (n=103)	Oral (n=103)	<i>p-</i> value	
Sex, n (%)				
Male	59 (57.3)	57 (55.3)	$0.888^{a}$	
Female	44 (42.7)	46 (44.7)		
Age, n (%)				
< 1 year old	17 (16.5)	8 (7.8)		
1-5 year old	38 (36.9)	27 (26.2)	0.058 <sup>a</sup>	
5-10 year old	23 (2.3)	29 (28.2)		
10-17 year old	25 (24.3)	39 (37.9)		
Type of diagnosis, n (%)				
Acute lymphoblastic leukemia	12 (11.7)	15 (14.6)		
Central nervous system infection	9 (8.7)	4 (3.9)		
Dengue fever	2 (1.9)	10 (9.7)	0.120 <sup>a</sup>	
Bronchopneumonia	8 (7.8)	2 (1.9)		
Acute tonsillopharyngitis	3 (2.9)	7 (6.8)		
Others	69 (67.0)	65 (63.1)		
Body weight, mean, kg (SB)	18.7 (12.95)	24.5 (14.92)	$0.060^{b}$	
Body height, mean, cm (SB)	104.9 (30.41)	115.9 (31.14)	0.028 <sup>b</sup>	
BMI, mean, kg/m <sup>2</sup> (SB)				
Malnutrition	86 (83.5)	77 (74.8)		
Normal nutrition	15 (14.6)	21 (20.4)	0.249 <sup>a</sup>	
Over nutrition	2 (1.9)	5 (4.9)		
Preliminary temperature, mean, °C (SB)	38.6 (0.42)	38.7 (0.46)	0.111 <sup>b</sup>	

<sup>\*</sup>Chi-square test.

administration, the average temperature dropped from  $38.6\pm0.42$  to  $38.3\pm0.45$ °C (p< 0.001) and after 180 minutes it reached  $37.1\pm0.36$ °C (p<0.001). Meanwhile in group 2, after 15 minutes, the average temperature reduced from  $38.7\pm0.46$ °C to  $38.0\pm3.74$ °C (p<0.001) and reached  $37.1\pm0.34$ °C after 180 minutes. Therefore, both treatments showed the same in reducing temperature at the end of therapy period.

In both intravenous and oral group, the side effect recorded was nausea. In intravenous group, one person experienced nausea after 30 minutes of paracetamol administration, while in the oral, one person experienced nausea after 60 minutes. In both groups, two people experienced nausea after 120 minutes. Other complaints, such as vomiting and erythema, were not found.

#### Discussion

Paracetamol is the widely used antipyretics in children. Antipyretics inhibit prostaglandin synthesis, acts mainly by inhibiting the formation of prostaglandin E2 in the brain. 7,12 Although both intravenous and oral paracetamol have proven effective in reducing fever, paracetamol administration to children with fever does not have uniformity yet. 2,3 World Health Organization (WHO) recommends the use of paracetamol when the temperature gets higher than 39.0°C, however, it does not recommended for routine use for children. 4

In this study, we found that the average temperature of intravenous group was 38.6°C and in oral group was 38.7°C with baseline axillary measurement. A study in

Table 2. Correlation between fever disappearance in intravenous and oral paracetamol.

	Paracetamol A			
Characteristic	Intravenous (n=103)	Oral (n=103)	<i>p-</i> value	
15 minutes				
No Fever	21 (20.4)	10 (9.7)	0.051	
Fever	82 (79.6)	93 (90.3)	0.051	
30 minutes				
No Fever	45 (43.7)	37 (35.9)	0.210	
Fever	58 (56.3)	66 (64.1)	0.319	
60 minutes				
No Fever	76 (73.8)	70 (68.0)	0.442	
Fever	27 (26.2)	33 (32.0)	0.443	
120 minutes				
No Fever	93 (90.3)	94 (91.3)	1 000	
Fever	10 (9.7)	9 (8.7)	1.000	
180 minutes				
No Fever	102 (99.0)	102 (99.0)	1.000	
Fever	1 (1.0)	1 (1.0)		

<sup>\*</sup>Chi-square test.

Chicago also discovered similar results.<sup>13</sup> Different results were demonstrated by a study in India which found that the temperature difference between before and after oral administration were 38.0°C to 39.8°C, examined using axillary termometer<sup>14</sup> The results of a study in USA showed wider temperature differences between before and after oral paracetamol (39.1°C), which was in line with the recommendation of American Academy of Pediatrics (AAP)

and National Institute for Health and Care Excellence (NICE) using rectal temperature measurement.<sup>15</sup>

In this study, there was no significant difference between the intravenous and oral paracetamol in nonfever groups. However, the results report that subjects with no fever had a higher prevalence than fever. Different results were demonstrated by a study done a study in Athena, intravenous paracetamol group showed fever was

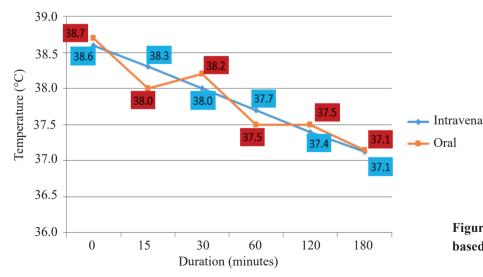


Figure 1. Average temperature based on the observation time.

Group (Observation Time)	Mean	Temperature Difference	SD	Confidence Interval (CI) 95%	<i>p-</i> value	
Intravenous Group						
0 minute	38.6	0	0.42	38.53 - 38.69	0.001*	
15 minutes	38.3	-0.3	0.45	38.23 - 38.41		
30 minutes	38.0	-0.6	0.46	37.95 - 38.13		
60 minutes	37.7	-0.9	0.47	37.64 - 37.83	0.001*	
120 minutes	37.4	-1.2	0.46	37.31 - 37.49		
180 minutes	37.1	-1.5	0.36	37.02 - 37.16		
Oral Group						
0 minute	38.7	0	0.46	38.62 - 38.80		
15 minutes	38.0	-0.7	3.74	37.29 - 38.76		
30 minutes	38.2	-0.5	1.09	37.99 - 38.42	0.001*	
60 minutes	37.5	-1.2	1.75	37.19 - 37.88	0.001*	
120 minutes	37.5	-1.2	0.42	37.42 - 37.58		
180 minutes	37.1	-1.6	0.34	37.07 - 37.21		

Table 3. Temperature difference at observation time between intravenous and oral paracetamol groups.

reduced by 73.2% patients in 3 hours.<sup>16</sup> In our study oral paracetamol administration in this research reduced fever faster than intravenous paracetamol administration at the first 15 minutes. A study in 2008 reported that paracetamol dose 15 mg/kg reduced fever faster by 1°C 30 minutes after oral paracetamol administration.<sup>17</sup> This phenomenon could happen because the absorption of oral paracetamol was significantly influenced by gastric emptying, foods in stomach could reduce the systemic absorption of oral paracetamol.<sup>18</sup>

Difference in temperature reduction during 180 minutes observation time were 1.5 in intravenous paracetamol and 1.6 in oral paracetamol subsequently. A study in Washington also obtained similar results oral. Panother study in USA in 2013 reported nearly similar results oral paracetamol showed temperature decreased after 30 minutes and it continued to lower until its maximum of 1.33°C after 3 hours. A study in Canada in 2002 found the initial temperature results before oral administration of paracetamol 39.2°C to 42.2°C. Different results was reported which higher temperature decreased in oral paracetamol after 180 minute. A study in Miami reported that intravenous paracetamol decreased temperature by 0.9°C after 180 minutes, showing different results with this study.

The side effect found was only nausea after 30 minutes and 60 minutes of intravenous and oral paracetamol administration, respectively. The research in San Diego in 2011 also obtained similar results.<sup>23</sup> A systemic review study in Qatar reported that intravenous paracetamol did not significantly deference ioavailability compared to oral paracetamol, and concluded that there were indication to give intravenous paracetamol amongs patients who actually could take oral paracetamol.<sup>24</sup> Different adverse effect found in this study might be caused by many factors, such as basic ailment, paracetamol administration when intestine is empty or after eating this is because paracetamol will inhibit the synthesis of cyclooxygenase and prostaglandin enzyme so that it leaves adverse effect in stomach.<sup>25</sup>

#### Conclusion

The administration of intravenous and oral paracetamol therapy seem to have same antipyretic effect to reduce fever with the doses 15 mg/kg. Oral route may be preferred because of its predictable rapid absorption, the intravenous seems to be a good and equal effective alternative in special condition such as vomiting, or condition preventing oral administration. Either intravenous or oral paracetamol gives the efficacy to reduce fever.

<sup>\*</sup>Repeated Measures, ANOVA.

# References

- Green RJ, Pentz A. Fever in children: how to minimize risk and provide appropriate therapy. S Afr Fam Pract. 2014; 56(4): 212-5.
- Sullivan JE, Farrar HC. Fever and antipyretics use in children. Pediatrics. 2011; 127(3): 580-7.
- El Radhi AS, Carrol J, Klein N. Clinical manual of fever in children. Berlin: Springer; 2009.
- World Health Organization. Integrated Management of Childhood Illness. Geneva: World Health Organization; 2000.
- El-Radhi AS. Why is the evidence not affecting the practice of fever management? Arch Dis Child. 2008; 93(11): 918-20.
- Hoque I, Chatterjee A, Bhattacharya S, Biswas R, Auddy S, Mondal K. A review on different types of the non steroidal anti-Inflammatory drugs (NSAIDs). Int J Adv Multidiscip Res. 2016; 3(9): 41-51.
- Plaisance KI, Mackowiak PA. Antipyretic therapy: Physiologic rationale, diagnostic implications, and clinical consequences. Arch Intern Med. 2000; 160(4): 449-56.
- Oscier C, Bosley N, Milner Q. Paracetamol A review of three routes of administration. Anaesth. 2007; 23: 112-4.
- Roy S, Simalti AK. Comparison of antipyretic efficacy of intravenous (IV) acetaminophen versus oral (PO) acetaminophen in the management of fever in children. Indian J Pediatr. 2018; 85(1): 1-4. doi: 10.1007/s12098-017-2457-3.
- Paramba FC, Naushad VA, Purayil N, Mohammed OH, Chandra P. Randomized controlled study of the antipyretic efficacy of oral paracetamol, intravenous paracetamol, and intramuscular diclofenac in patients presenting with fever to the emergency department. Ther Clin Risk Manag. 2013; 9: 371-6.
- Aronoff DM, Neilson EG. Antipyretics: mechanisms of action and clinical use in fever suppression. Am J Med. 2001; 111(4): 304-15
- Feverish illness in children. Assesment and management in children younger than 5 years. London: National Institute for Health and Clinical Excellene; 2007.
- 13. Peacock WF, Breitmeyer JB, Pan C, Smith WB, Royal MA.

  A randomized study of the efficacy and safety of intravenous acetaminophen compared to oral acetaminophen for treatment of fever. Acad Emergency Med. 2011; 18(4): 360-6.

- Gupta H, Shah D, Gupta P, Sharma KK. Role of paracetamol in treatment of childhood fever: A double-blind randomized placebo controlled trial. Indian Pediatrics. 2007; 44(12): 903-11.
- Jayawardena S, Kellstein D. Antipyretic efficacy and safety of ibuprofen versus acetaminophen suspension in febrile children: Results of 2 randomized, double-blind, single-dose studies. Clin Pediatr. 2017; 56(12): 1120-7.
- Bourboulis EJ, Spyridaki A, Savva A, Georgitsi M, Tsaganos T, Mauktaroudi M, et al. Intravenous paracetamol as an antipyretic and analgesic Medication: the significance of drug metabolism. J Pharmacol Sci. 2014; 124(2): 144-52.
- Gibb IA, Arderson BJ. Paracetamol (acetaminophen) pharmacodynamics: interpreting the plasma concentration. Arch Dis Child. 2008; 93: 241-7.
- Divoll M, Greenblatt DJ, Ameer B, Abernethy DR. Effect of food on acetaminophen absorption in young and erderly subjects. J Clin Pharmacol. 1982; 22(11-12): 571-6.
- Temple AR, Zimmerman B, Gelotte C, Kuffner EK. Comparison of the efficacy and safety of 2 acetaminophen dosing regimens in febrile infants and children: a report on 3 legacy dtudies. J Pediatr Pharmacol Ther. 2017; 22(1): 22-32.
- Temple AR, Temple BR, Kuffner EK. Dosing and antipyretic efficacy of oral acetaminophen in children. Clin Ther. 2013; 35(9): 1361-75.
- Scolnik D, Kozer Z, Jacobson S, Diamond, Young NL. Comparison of oral versus normal and high-dose rectal acetaminophen in the treatment of febrile children. Pediatrics. 2002; 110(3): 553-6.
- 22. Kett DH, Breitmeyer JB, Ang R, Royal MA. A Randomized study of the efficacy and safety of intravenous acetaminophen vs. intravenous placebo for the treatment of fever. Clin Pharmacol Ther. 2011; 90(1): 32-9.
- Fox ER, Jones VM, Beckwith MC. Acetaminophen injection: A review of clinical information including forms not available in the United States. J Pain Palliat Care Pharmacother. 2012; 26: 115-7.
- Jibril F, Sharaby S, Mohammed A, Wilby KJ. Intravenous versus oral acetaminophen for pain: systematic review of current evidence to support clinical decision-making. Can J Hosp Pharm. 2015; 68(3): 238-4.
- Graham GG, Scott KF, Day RO. Tolerability of paracetamol. Drug safety. 2005; 28(3): 227-40.