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PUBLICATION TYPE

Journals

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2009-2021

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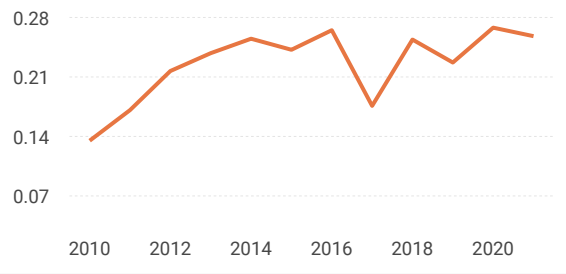

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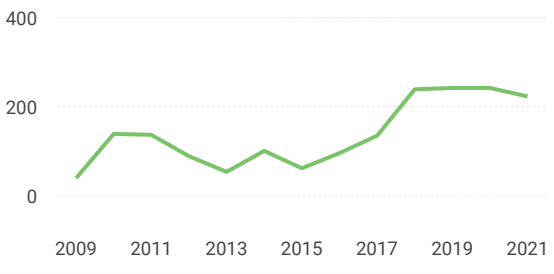

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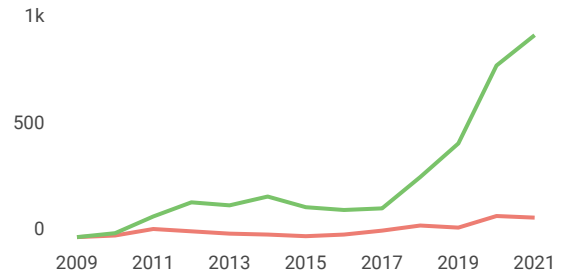

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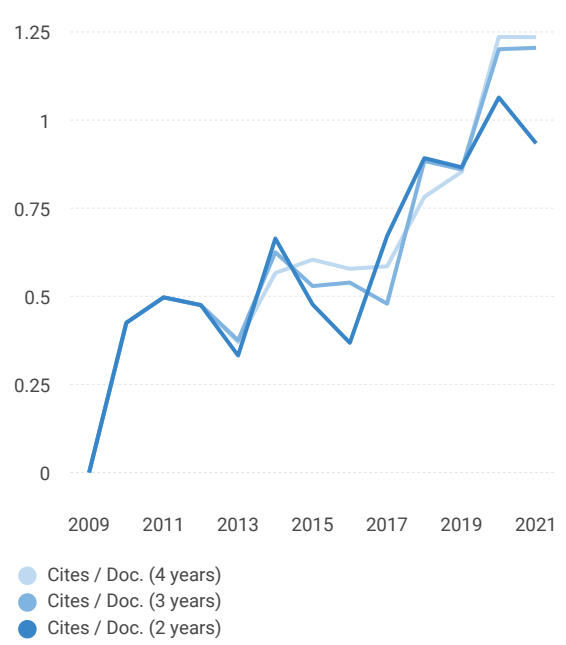

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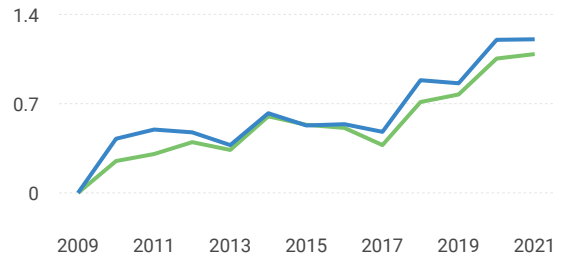

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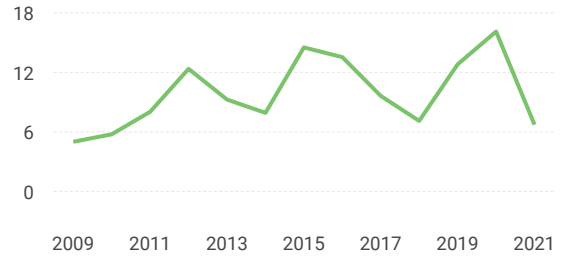

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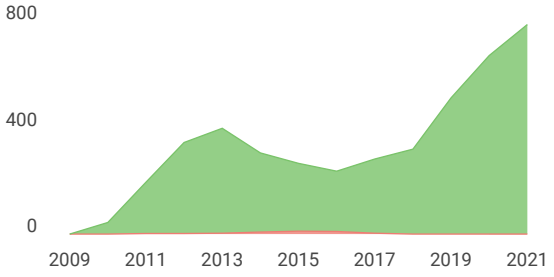

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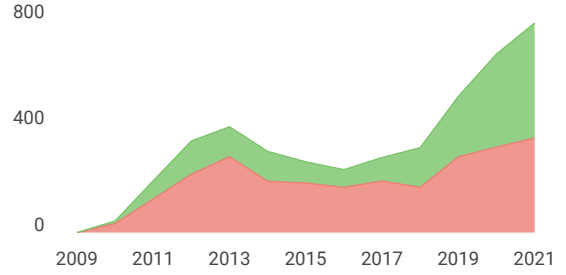

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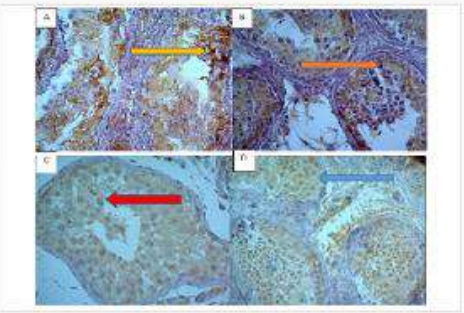

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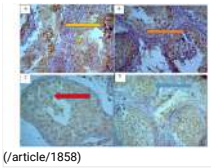
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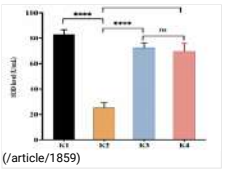
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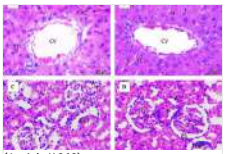
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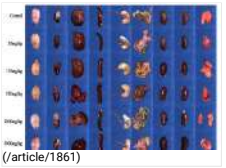
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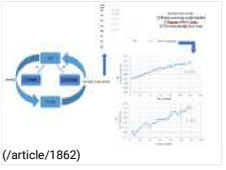
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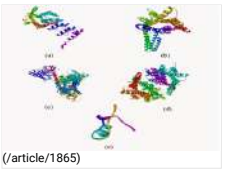
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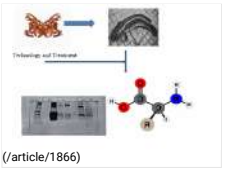
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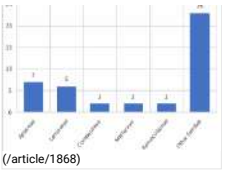
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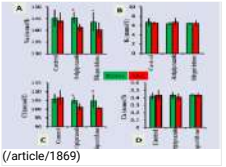
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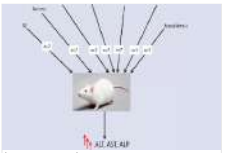
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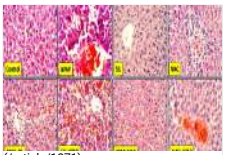
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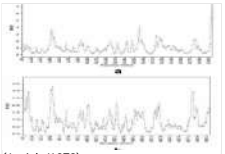
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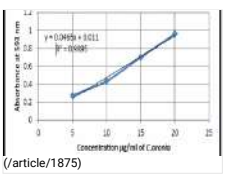
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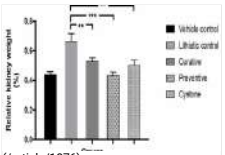

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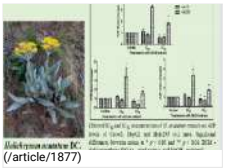
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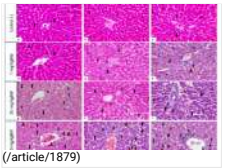
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Analysis Protein APOB and TroponinT in Obese Mice (Musmusculus) Induced by Static Magnetic Field as a Marker of Coronary Heart (/article/1880)

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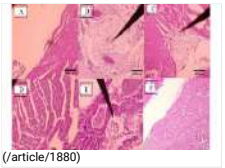
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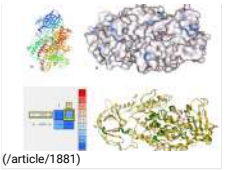
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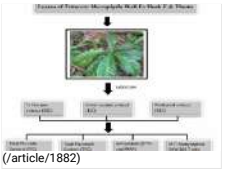
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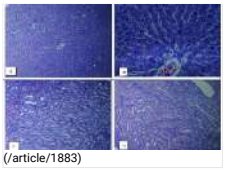
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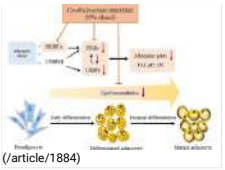
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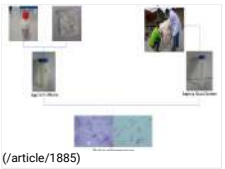
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Original Article

Efficacy and Tolerability of Intravenous Paracetamol Compared to Oral Paracetamol for the Treatment of Childhood Fever

Prastiya Indra Gunawan*, Darto Saharso

ABSTRACT

Introduction: Paracetamol is widely used as antipiretic in children and has complete rute. The use of enteral rute is limited because of high variability of bioavailability. Intravenous paracetamol commonly used as accessible analgetic in adult. There are limited data about efficacy and tolerability intravenous paracetamol compares to oral paracetamol as antipiretic in children. The aim of the study is to analyse efficacy and tolerability intravenous paracetamol compared to oral paracetamol for treating fever in children. **Methods:** A randomized, controlled, and open labelled clinical trial was conducted at pediatric ward Soetomo hospital Surabaya. Eligible patients received either intravenous paracetamol or oral paracetamol 10 mg/kgBW and were examined for temperature at 15, 30, 45, 60, 120, 180 and 240 minutes. Tolerability evaluations included adverse event (AE), physical exam and laboratory assessments. **Results:** Of 104 patients, 52 received intravenous paracetamol intravena and 52 received oral paracetamol. Mean temperature intravenous group were lower than oral groups, with higher degree of decrease. The difference were achieved at 30, 45, and 60 minutes with p=0.005, 0.002, and 0.006 respectively. Maximum decrease from baseline were achieved at 120-minute for intravenous grup and 180-minute for oral groups. Normal temperature achievement were higher in intravenous group than oral. The adverse event were comparable between the intravenous and oral groups. **Conclusion:** Intravenous paracetamol is more effective and as safe as oral paracetamol in reducing fever in children.
Key words: Accessible, Efficacy, Fever, Intravenous paracetamol, Tolerability.

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INTRODUCTION

Paracetamol is widely used to reduce fever in children. The use of oral paracetamol is limited in patients who are unable to take oral medication. While the use of rectal route is also limited because of high variations of bioavailability.[1] Study by Peterson showed low plasma concentrations after administration of rectal paracetamol and did not even reach the target concentration to give therapeutic effect.[2,3] Because of the limitations of enteral drugs, we conducted this study to analyze the effectiveness and safety of intravenous paracetamol to reduce fever in children.

Fever is 20-30% of the complaints that bring patients to the doctor due to parent's anxiety. Fever has beneficial effects but can cause discomfort in children, increasing metabolism activity, oxygen consumption and carbon dioxide production, and increased heart rate 10-15 beats/min/degree temperature increase. In such condition like encephalitis or cerebral abscess sometimes fever difficult to treat.[4,5]

Paracetamol is the safest antipyretic used in children and has complete route of administration.[6-9] Research on adults suggests the administration of accessible intravenous paracetamol is more effective than oral paracetamol and well tolerated in patients with fever due to endotoxin, but limited data on the use of intravenous paracetamol in children.[10] In children, administration of intravenous paracetamol were also more effective than the administration of rectal paracetamol. There were much available data on its use as an antipyretic and analgesic in adult, but limited data on comparing the efficacy and tolerability of intravenous paracetamol compared to oral paracetamol as an antipyretic in febrile children.[11] The purpose of this study was to analyse efficacy and tolerability intravenous paracetamol compares to oral paracetamol for treating fever in children.

MATERIAL AND METHODS

Patients

The regional ethics committee of Soetomo General Academic Hospital approved this randomized, controlled, and open-labeled clinical trial. Comprehensive informed consent was obtained from the legal representative of the patient. The study was conducted at Pediatric ward from February - June 26, 2016. Inclusion criteria were patients with a temperature $\geq$ 38^{0}C (tympanic membrane thermometer), age > 6 months, and signed informed consent. Patients were excluded if they were taking antipyretics within 4 hours, temperature >40^{0}C, decreased consciousness, dehydration, history of paracetamol allergy, hepatic dysfunction, central nervous system disorders, impaired kidney function, and critically ill.

METHODS

Patients received intravenous paracetamol or paracetamol oral 10 mg/kgBW with random allocation. The body temperature was measured at 15, 30, 45, 60, 120, 180, and 240 minutes after paracetamol administration and rated the onset and degree of temperature reduction, time of normal temperature achievement. Temperature 36.6 - 37.8°C by tympanic membrane thermometer was defined as

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normal temperature. Adverse events were observed until 24 hours after drug administration from clinical and laboratory assessment. When the patient's body temperature increases reach >40°C, the patient is accounted to drop out, and physical treatment or other medication were allowed.

Statistical analysis

t-test was used for measuring the degree of temperature reduction, chi-square test for clinical adverse events, Wilcoxon-signed rank test and Mann-whitney for laboratory changes, and the log rank test time needed to achieve normal temperature, with significance level of 5%.

RESULTS

Of 104 patients enrolled this study, 52 received intravenous paracetamol and 52 received oral paracetamol. During the observation, two patient dropped out. One patient dropped out because of hypovolemic shock event caused by dengue hemorrhagic fever (DHF) and one patient suffered from hyperpyrexia. Patient with DHF was then received fluid resuscitation therapy. Whereas Patient who experienced an increase in temperature up to 41^0 C treated with surface cooling and metamizol injection.

The baseline characteristics in both study groups are similar with p value >0.05 as shown in table 1. Table 1 also describes the initial temperature, room temperature, nutritional status, diagnosis, the use of intravenous fluids, the mean of paracetamol dose/day, and the use of other hepatotoxic drugs.

Efficacy

Significant differences of temperature measurements of both groups occurred at 30, 45 and 60 minutes with p=0.005, 0.002, and 0.006 respectively. After the 3rd hour, temperature reduction was no longer occurred, and even tended to rise. The mean body temperature in patients who received intravenous paracetamol was lower than oral paracetamol. (Figure 1)

Temperature reduction after administration of paracetamol in both groups started to differ significantly from previous measurements at different times. In the intravenous group, significant differences have occurred at 15 minutes after drug, as much as -0.1423 (±0.339) °C with P=0.004. In the oral group, significant difference at 30 minutes after drug, as much as -0.239 (±0.282) °C with p=0.000. (Table 2)

Degree in temperature reduction from initial temperature differs significantly from 15 minutes after drug administration, with a greater reduction occurred in the intravenous group. Level of significance at minute 15, 30, 45, 60, and 120 are 0.038; 0.000, 0.000, 0.000 and 0.019 respectively. (Table 3) As shown in table 3, the temperature reduction continues and significantly different in both groups until the third hour. The highest temperature reduction form baseline in the intravenous paracetamol group achieved in the second hour after drug administration, whereas oral paracetamol group achieved at the third. Temperature reduction at the 3rd and 4th after administration of intravenous paracetamol did not differ significantly compared to oral paracetamol group.

More patients achieved normal temperatures in intravenous group compared to oral group. Significant differences in both groups occurred at 30, 45 and 120 minutes after administration of paracetamol. Frequency of normal temperatures began to decline at the 3rd and 4th after the administration of paracetamol. (Figure 2)

In this study, there were five (9.6%) patients in the intravenous paracetamol group and 16 (30.8%) patients on oral paracetamol group who never reaches normal temperature. Based on an analysis using the logrank test, intravenous paracetamol group achieved normal temperature faster than the oral groups. The mean time of normal temperature achievement was 74.043 (±7.029) minutes for intravenous group and 96.250 (±9.989) minutes for oral groups p=0.048. (Figure 3)

Table 1: Baseline characteristic of the patients.

	Intravenous Paracetamol	Oral Paracetamol	P
Sex, n (%)			
- Male	30 (57.7)	25 (48.1)	0.326
- Female	22 (42.3)	27 (51.9)	
Age, mean months (SD)	56.85 (41.155)	59.08 (46.381)	0.796
Body weight, kg,mean (SD)	15.619 (7.932)	15.888 (9.218)	0.186
Body height, cm,mean (SD)	101.9 (23.41)	101.0 (26.10)	0.268
Nutritional status, n (%)			
- Obesity	0	2 (3.8)	0.944
- Overweight	2 (3.8)	2 (3.8)	
- Good	23 (44.2)	22 (42.4)	
- Moderate malnutrition	24 (46.2)	20 (38.4)	
- Severe malnutrition	3 (5.8)	6 (11.6)	
Baseline temperature (SD)	38.937 (0.519)	38.860 (0.440)	0.417
Diagnosis, n (%)			
- Bronkopneumonia	11 (21.2)	8 (15.4)	
- Dengue infection	10 (19.2)	8 (15.4)	
- Acute Pharyngitis	12 (23.1)	14 (26.9)	
- Diarrhea	7 (13.5)	10 (19.2)	
- Tuberculosis	2 (3.8)	1 (1.9)	
- UTI	3 (5.8)	1 (1.9)	
- Typhoid fever	2 (3.8)	3 (5.8)	
- Malignancy	4 (7.7)	6 (11.5)	
- Other	1 (1.9)	1 (1.9)	
Room temperature, mean (SD)	30.279 (0.791)	30.404 (1.36)	0.568
Antibiotic, n (%)	32 (61.5)	32 (61.5)	1.000
Intravenous fluid, n (%)	43 (82)	42 (80.7)	1.000
Paracetamol dose, mean, mg/kg/day (SD)	24.84 (11.79)	24.0 (16.74)	0.765
Other hepatotocsic drugs, n (%)	1 (1.9)	3 (5.7)	0.618

Significant at p <0.05 by chi-square test statistic for sex, antibiotics, intravenous fluids and diagnosis; independent sample t test for age, weight, height, initial temperature, room temperature; Mann-Whitney test for nutritional status

Table 2: Comparison of mean temperature reduction from previous measurements.

	Termperature reduction			
	IV paracetamol	P	Oral paracetamol	p
t0 - t1	-0.142 (±0.339)	0.004*	-0.023 (±0.228)	0.469
t1 - t2	-0.502 (±0.333)	0.000*	-0.239 (±0.282)	0.000*
t2 - t3	-0.264 (±0.352)	0.000*	-0.200 (±0.281)	0.000*
t3 - t4	-0.183 (±0.313)	0.000*	-0.198 (±0.323)	0.000*
t4 - t5	-0.356 (±0.554)	0.000*	-0.435 (±0.488)	0.000*
t5 - t6	0.053 (±0.556)	0.500	-0.086 (±0.447)	0.174
t6 - t7	0.214 (±0.386)	0.000	0.139 (±0.420)	0.022

*Significant at p <0.05 by independent sample t test

Table 3: The mean temperature reduction from baseline.

	Temperature reduction iv paracetamol	Temperature reduction oral paracetamol	p
t0 - t1	-0.142 (±0.339)	-0.023 (±0.228)	0.038*
t0 - t2	-0.644 (±0.420)	-0.262 (±0.372)	0.000*
t0 - t3	-0.908 (±0.476)	-0.462 (±0.453)	0.000*
t0 - t4	-1.090 (±0.579)	-0.660 (±0.600)	0.000*
t0 - t5	-1.446 (±0.678)	-1.094 (±0.816)	0.019*
t0 - t6	-1.394 (±0.750)	-1.192 (±0.842)	0.204
t0 - t7	-1.180 (±0.784)	-1.053 (±0.862)	0.439

*Significant at p <0.05 by independent sample t test

Tolerability

There were no significant differences between the incidence of adverse events of intravenous paracetamol group compared to oral paracetamol. Vomiting occurred in one patient from intravenous groups and one patient from oraloral group, which improved without treatment. Nausea is experienced by 1 patient in intravenous group and 5 patients in oral group, which also improved without treatment. Intravenous access irritation experienced by 2 patients in the oral group, as a result of phlebitis and improved after the removal of intravenous access. Differences in AST and ALT changes in both groups were analyzed by Mann-Whitney test because the changes are not normally distributed. From this test, there was no significant differences in AST and ALT changes in both groups with p value 0.354 for AST and 0.071 for ALT (p> 0.05).

DISCUSSION

Temperature reduction from previous measurements in the intravenous group, started significantly since the 15th minute, while in the oral group achieved longer, which in the 30th minute. Difference onset of temperature reduction is due to the difference time to achieve plasma concentration of intravenous and oral paracetamol. The plasma concentration of paracetamol ranging from 10-20 mg/ml or 0.06 to 0.13 mmol/L to obtain antipyretic effect.[12] Oral paracetamol is well absorbed and begin to affect approximately 0.5 to 1 hour after administration, after reach plasma concentration.[13] Faster onset of action after administration of intravenous paracetamol compared to oral and rectal paracetamol has been demonstrated in previous studies, since intravenous paracetamol plasma concentration achieved more rapid therapeutic effect, 15 minutes after administration and more predictable.[14-16]

Mean body temperature after administration in patients received intravenous paracetamol was lower than oral paracetamol and these differences begin to emerge in the 30th minute measurement. As for the degree of temperature reduction from baseline in the two groups differed significantly at 15 minutes after drug administration, with a greater reduction occurred in the intravenous group. The highest temperature reduction in the intravenous paracetamol group achieved at the second hour after drug administration, whereas oral paracetamol group achieved at the third. Temperature reduction did not differ significantly at the third and fourth hour after drug administration, because the half-life of the drug is the same, although the route is different.[13,17] This is consistent with research by Duhamel, and Peacock. Intravenous paracetamol plasma concentration is achieved faster, which is 15 minutes after administration. Temperature reduction after administration of intravenous paracetamol was greater than the oral route, especially in the first two hours. After that, different temperature reduction did not observe between two groups, although temperature reached remained lower in the intravenous group. In adult patient's post-surgery, oral paracetamol gives greater plasma concentrations variation than intravenous administration. Plasma concentration after oral administration of paracetamol increases with dose and time, and have higher inter individual differences.[15,18]

More patients achieved normal temperatures in intravenous group compared to oral group with significant differences occurred in the 30th, 45th and 120th minutes after drug administration. Frequency of normal temperatures began to decline at the 3rd and 4th after the administration of paracetamol. This is caused by an increase in temperature reduction in intravenous group increased greater in the 30th minute and remained stable in the next minute. While temperature reduction in the oral group was increased as the concentration of plasma after oral administration increases with time, with large inter individual differences resulting in less predictable, especially at the first 80 minutes.[10] Normal temperatures in the intravenous group in this study was achieved faster than oral group as it decreased more rapidly. This effect can be predicted because of effect stability due to low variations of intravenous paracetamol bioavailability.[11]

Research on the tolerability of paracetamol has been widely performed.[3,8,9,15,19] Tolerability, in the form of adverse event of intravenous and oral administration of paracetamol evaluated in this study, did not show significant differences. Nausea and vomiting in this study could be caused by given drug or by the underlying disease. In patients who received oral paracetamol, vomiting caused by the bitter taste of the drugs. Patients experienced nausea may result from the underlying because of nausea was observed prior to drug administration. Irritations found in two patients in the oral group due to phlebitis. Clinical adverse events did not differ between the two groups. These finding were consistent with previous research by Kett which compared intravenous paracetamol to placebo intravenously with randomized clinical trials, double blind. The adverse event of intravenous paracetamol administration had no different than placebo intravena.[16]

Transaminase levels post-administration of paracetamol in this study was within normal limits, or mild increase without clinical symptoms because the daily dose of paracetamol in both groups was within allowance dose. The highest levels of aminotransferase were AST 351 IU/L, in patients who received palliative treatment with paracetamol dose of 93.33 mg/kg/day. Three days after cessation of paracetamol, the transaminase lever was re-examined and resulted in normal limit without treatment. While the highest levels of ALT were 194 IU/L in patients with sepsis and declined as the underlying disease improved. Hepatotoxicity incidence, generally occur at multiple dosing with a total dose higher than the allowance dose.[20]

Obstacle in this study was the difficulty in calculating the fluid consumption. Fluid consumption is not possible to quantify because of many patients were received breastfeeding. However, all study patients were in a good hydration status, none of them are dehydrated during the observation. Patient who did not only receive one-time paracetamol was another obstacle in this study, because they still had fever for 24 hours of observation. Therefore, the total paracetamol dose the patient received per kg BW were analyzed, and the results are homogeneous with no differences between the two treatment groups.

CONCLUSION

Intravenous paracetamol in children has a better efficacy than oral paracetamol as an antipyretic and well tolerated. Therefore, intravenous paracetamol can be considered as an alternative to the guidelines in the treatment of fever in children.

CONFLICTS OF INTEREST

The authors declare to have no conflicts of interest relevant to this article.

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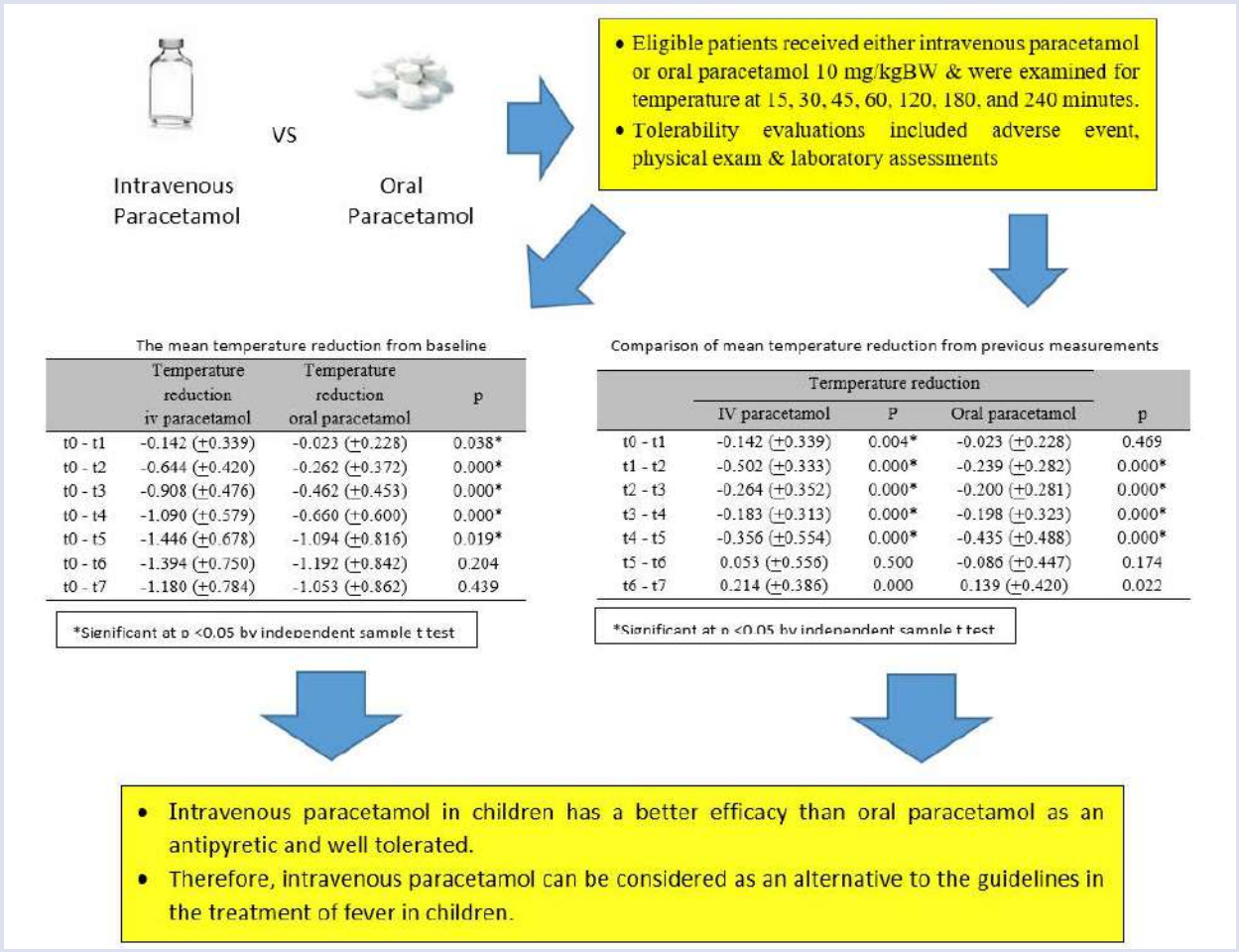
GRAPHICAL ABSTRACT



The mean temperature reduction from baseline

	Temperature reduction iv paracetamol	Temperature reduction oral paracetamol	p
t0 - t1	-0.142 (±0.339)	-0.023 (±0.228)	0.038*
t0 - t2	-0.644 (±0.420)	-0.262 (±0.372)	0.000*
t0 - t3	-0.908 (±0.476)	-0.462 (±0.453)	0.000*
t0 - t4	-1.090 (±0.579)	-0.660 (±0.600)	0.000*
t0 - t5	-1.446 (±0.678)	-1.094 (±0.816)	0.019*
t0 - t6	-1.394 (±0.750)	-1.192 (±0.842)	0.204
t0 - t7	-1.180 (±0.784)	-1.053 (±0.862)	0.439

Comparison of mean temperature reduction from previous measurements

	Termperature reduction			
	IV paracetamol	P	Oral paracetamol	p
t0 - t1	-0.142 (±0.339)	0.004*	-0.023 (±0.228)	0.469
t1 - t2	-0.502 (±0.333)	0.000*	-0.239 (±0.282)	0.000*
t2 - t3	-0.264 (±0.352)	0.000*	-0.200 (±0.281)	0.000*
t3 - t4	-0.183 (±0.313)	0.000*	-0.198 (±0.323)	0.000*
t4 - t5	-0.356 (±0.554)	0.000*	-0.435 (±0.488)	0.000*
t5 - t6	0.053 (±0.556)	0.500	-0.086 (±0.447)	0.174
t6 - t7	0.214 (±0.386)	0.000	0.139 (±0.420)	0.022

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