

Comparison of High Loading Dose Versus Usual Dose of Rectal Acetaminophen in the Treatment of Febrile Children

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ABSTRACT

Background: The superiority of antipyretic efficacy of high dose rectal acetaminophen is not well established yet.

Objectives: The present study aimed to compare the antipyretic effectiveness of high loading dose (30 mg/kg) and standard dose (15mg/kg) of rectal acetaminophen in febrile children.

Patients and Methods: This triple blind randomized clinical trial was conducted on 76 patients aged 6 months to 6 years with rectal temperature of $> 39^{\circ}\text{C}$ who had been referred to 17th Shahrivar training hospital of Rasht, Guilan, Iran. The patients were assigned to one of two groups: First group ($n = 37$ patients) received 15 mg/kg and the second group ($n = 39$ patients) received 30 mg/kg of acetaminophen rectally. The patient's rectal temperatures were measured before rectal acetaminophen administration and one and three hours post administration using Microlife rectal digital thermometer (Sweden) and were compared between the two groups.

Results: One hour after rectal administration of acetaminophen the mean temperature changes in groups 1 and 2 were $0.97 \pm 0.59^{\circ}\text{C}$ and $1.03 \pm 0.62^{\circ}\text{C}$, respectively (P value = 0.663). A significant difference was seen in the mean temperature reduction between the two groups three hour after treatment ($1.22 \pm 0.72^{\circ}\text{C}$ vs. $1.57 \pm 0.65^{\circ}\text{C}$, respectively; P value = 0.028).

Conclusions: In febrile children, administration of 30 mg/kg of rectal acetaminophen as the loading dose may be more effective than the standard dose in reducing fever after 3 hours of medication.

Keywords: Acetaminophen; Child; Fever; Administration, Rectal

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►Article type: Research Article; Received: 19 Jan 2013, Revised: 29 Jan 2013, Accepted: 08 Apr 2013; DOI: 10.5812/pedinflect.10350

►Implication for health policy/practice/research/medical education:

This research project was conducted from May 2009 to September 2010. The superiority of antipyretic efficacy of high dose rectal acetaminophen is not well established yet. On the basis of this study, we found that in febrile children, administration of 30 mg/kg of rectal acetaminophen may be more effective than the standard dose in reducing fever.

►Please cite this paper as:

Hashemian H, Momtazbakhsh M, Atrkar Roshan Z. Comparison of High Loading Dose Versus Usual Dose of Rectal Acetaminophen in the Treatment of Febrile Children. Arch Pediatr Infect Dis.2013;1(3): 126-30. DOI: 10.5812/pedinflect.10350

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1. Background

Fever is a common symptom in children and is believed to constitute 25 to 30% of medical and emergency room visits annually (1-3). It has been shown that a rectal temperature of less than 39°C does not need treatment (3-5). Moreover, world health organization emphasizes a fever of more than 39°C which produces complications for the patients, requires medical attention (6). It seems that judgment regarding the appropriate indication of fever reduction mostly relies on each patient's medical condition. In addition, choosing the appropriate fever treatment has been a challenging issue for a long time.

Antipyretic effects of acetaminophen are equal to that of aspirin. Besides, it does not have the side effects on the gastrointestinal system and platelets function. Considering these advantages made acetaminophen the preferred treatment of choice for the reduction of fever in children (1, 3, 4).

Acetaminophen is generally administered in standard doses of 10-15 mg/kg either rectally or orally (3, 4). Though there is no general consensus on rectal acetaminophen as the preferred choice of route, in some situations where oral preparation cannot be administered such as in a vomiting child or due to the preferences of parents or the physician, administration of the drug via rectum is inevitable (7). Moreover, pharmacokinetic properties of single dose of oral acetaminophen are known (8, 9). Nevertheless, pharmacokinetics of its single rectal dose is not well established since its absorption is prolonged and depends on size of suppository, base composition, and rate of dissolutions (10). Although several investigations have been conducted on acetaminophen, it is not known whether different doses of rectal acetaminophen have similar effects in reducing fever. Previous literature revealed that serum concentration of 15-20 µg/mL, which is considered as the therapeutic plasma level for antipyretic effect, could not be achieved by rectal dose of 10-15 mg/kg and a rectal dose of 30-45 mg/kg was needed (8-14). The maximum recommended daily dose of acetaminophen for children is 90 mg/kg/day (15). Toxic dose of acetaminophen is above 150 mg/kg/day or 12 g/day (16) and various studies about high loading dose acetaminophen use in children showed no obvious complications (1, 2, 7, 13).

2. Objectives

Since the antipyretic effect of acetaminophen is dose-dependent and also the general consensus regarding the efficacy of high loading dose versus low dose rectal acetaminophen is lacking, this study was designed to compare the antipyretic effectiveness of the standard dose of 15 mg/kg rectal acetaminophen versus a 30 mg/kg dose.

3. Patients and Methods

3.1. Study Population

This triple blind (patients, physician, and statistical analyzer) randomized clinical trial was conducted on 76 consecutive febrile children 6 months to 6 years old who had been referred to 17th Shahrivar hospital of Rasht, Iran during May 2009 and September 2010 with rectal temperatures of 39°C to 40.5°C in the prior 24 hours and had no other signs in the physical exam. Patients with a history of diarrhea, malignancy, renal or liver failure, neurologic disorders, seizure, vasculitis, allergy to acetaminophen and who evacuated suppository during the first 30 minutes, or had received acetaminophen in the previous 4 hours were excluded from the study. We included patients with rectal temperatures of 39°C and above. The study was approved by the research and ethics committee of Guilan university of medical sciences and written informed consent was obtained from the parents of all patients. The registration ID was IRCT138806182438N1.

The patients were randomly sorted into two groups. Thirty-seven patients took 15 mg/kg (low dose) and thirty-nine patients took 30 mg/kg (high dose) of rectal acetaminophen. Of these, 9 patients (24.3%) from the first group (low-dose group) and 11 patients (28.2%) from the second group (high-dose group) used oral antibiotics more than 8 hours prior to the study.

3.2. Study Maneuver

Patients were assigned to one of the two groups by using the random fixed block method. Four sample sealed packets (aabb, abab, abba, etc.) were designed. packets were chosen by-lot and patients were assigned to one of the two groups as the order of samples of each packet. Rectal acetaminophen was administered in lipophilic suppository form (Darou Pakhsh pharmaceutical manufacturing Co., Tehran, Iran). The 125 mg and 325 mg suppositories were cut in half or quarter longitudinally using a digital balance when necessitated.

A fixed trained nurse inserted the prepared suppository beyond the internal sphincter after lubrication. The patient's rectal temperatures were measured before rectal acetaminophen administration and one and three hours after, using Microlife rectal digital thermometer (Sweden) by a fixed pediatric resident who was blind to the patients' groups. The patients were placed in the prone position and the rectal thermometer was inserted into their rectums (2 to 2.5 cm). After hearing the beep of the thermometer, patients' rectal temperatures were read and recorded and were then compared between the two groups. Patients stayed in the emergency room until 3 hours after acetaminophen consumption (end of the study) and no another intervention was made to control their fever.

3.3. Statistical Analysis

The sample size was estimated on the basis of a pilot study on 20 consecutive febrile children between the ages of 6 months and 6 years who had visited the 17th Shahrivar hospital of Rasht, Iran. The patients were sorted into two equal groups (low dose and high dose rectal acetaminophen). Then, the sample size was calculated to be 40 for each group as shown below:

$$(Z_{1-\alpha} + Z_{1-\beta})^2 (S_1^2 + S_2^2) / (\mu_1 - \mu_2)^2 = (1.96 + 1.28)^2 (0.3^2 + 0.25^2) / (39.4 - 39.6)^2 = 40$$

The analyzer was also blind. Statistical analysis was performed using the SPSS V.14 software. For each of the measured variables or indexes, descriptive values were expressed as the mean \pm SD. All data were initially analyzed using the Kolmogorov-Smirnov test to assess for normal-

ity. Normally distributed numerical data were compared between groups using independent sample T and paired sample T tests. Discrete variables were analyzed using the chi-square analysis. All P-values were two-tailed and $P < 0.05$ was considered statistically significant.

4. Results

There were 31 girls (40.8%) and 45 boys with mean age 25.3 ± 17.7 months (range: 6-72 months), mean body weight 12.6 ± 3.7 kg (range: 6.3-21 kg) and mean rectal temperature 39.72 ± 0.40 °C (median: 39.5 °C and range: 39-40.5°C). No significant difference was shown between these characters in the group of patients treated with high dose versus the group treated with low dose rectal acetaminophen (Table 1).

Table 1. Demographic Data of the Patients in the Two Groups Receiving Low Dose (15 mg/Kg) Versus High Dose (30 mg/Kg) of Rectal Acetaminophen

Data	Low Dose (15 mg/kg)	High Dose (30 mg/kg)	P.value
Gender			0.672
Boys, No. (%)	21 (56.8)	24 (61.5)	
Girls, No. (%)	16 (43.2)	15 (38.5)	
Age (mo)	23 \pm 17	27.5 \pm 18.4	0.265
Weight (kg)	12.2 \pm 3.8	12.9 \pm 3.6	0.397

Table 2. Data of the Patients at Baseline, One and Three Hours After Treatment, Receiving Low Dose (15 mg/kg) Versus High Dose (30 mg/kg) of Rectal Acetaminophen

Data	Low Dose (15 mg/kg)	High Dose (30 mg/kg)	P.value
Mean body temperature at the onset of study	39.63 \pm 0.41°C	39.80 \pm 0.37°C	0.063
Mean body temperature one hour after treatment	38.66 \pm 0.64°C	38.77 \pm 0.60°C	0.443
Mean of body temperature change one hour after treatment	-0.97 \pm 0.59°C	-1.03°C \pm 0.62°C	0.663
Mean of body temperature 3 hours after treatment	38.41 \pm 0.69°C	38.23 \pm 0.65°C	0.238
Mean of body temperature change during 3 hours after treatment	-1.22 \pm 0.72°C	-1.57 \pm 0.65°C	0.028
At least 2°C decrease in body temperature one hour after treatment, No. (%)			0.746
Yes	3 (8.1)	4 (10.3)	
No	34 (91.9)	35 (89.7)	
At least 2°C decrease in body temperature 3 hours after treatment, No. (%)			0.05
Yes	6 (16.2)	14 (35.9)	
No	31 (83.8)	25 (64.1)	

All patients tolerated a high dose acetaminophen very well and no obvious complication occurred. Based on the parents' reports, nine (24.3%) out of 37 children treated with low dose rectal acetaminophen and 11 (28.2%) out of 39 children treated with high dose rectal acetaminophen had received oral antibiotic eight hours prior to the study.

5. Discussion

According to the findings of the present study, one and three hours after administration of both low dose and high dose rectal acetaminophen, the reduction of body temperatures of the patients were conspicuous. As shown in Table 2, our study showed that there was no sta-

tistically significant difference between the mean body temperatures of these two groups at one and three hour intervals after treatment. Although, mean temperature reductions three hours after treatment were higher in patients administered a high dose rectal acetaminophen comparing to the patients treated with a low dose acetaminophen. After one hour, the frequency of patients who showed a 2°C decrease in their body temperature was not different in the two groups but this difference was significant three hours after treatment (P value = 0.05).

The results of the studies by Howell and Patel (17) and Beck et al. (18) showed plasma levels of acetaminophen were significantly higher in patients receiving a higher dose of acetaminophen with increased duration of drug action. Furthermore, the results of a study by Hahn et al. (11) on 23 children at ages 9 weeks to 11 years showed that the time needed to reach the therapeutic serum level was shorter when a higher dose of rectal acetaminophen was used. Results of these studies agree with our results regarding a higher efficacy of high dose rectal acetaminophen compared to the lower doses.

Treñluyer et al. (2) in a randomized clinical trial on 121 children aged 4 months to 9 years compared the antipyretic effects of two doses of 30mg/kg and 15mg/kg of oral acetaminophen. The duration required to obtain a temperature lower than 38.5°C was significantly shorter, the maximum temperature decrease was significantly higher, and duration of rectal temperature below 38.5°C was significantly longer in the 30-mg/kg than in the 15-mg/kg group. These data suggest that acetaminophen treatment of fever may be more efficient with a higher loading dose and are compatible to our findings.

Golestan et al. (19) in a parallel group, randomized clinical trial on 60 febrile patients, 6 month to 6 years old, compared the antipyretic effects of two doses of 15mg/kg and 10mg/kg of oral acetaminophen. The rate of temperature reduction at the first and third hour post administration in group 1 (15mg/kg) was significantly higher. The authors concluded acetaminophen with dose of 15mg/kg is more effective in reducing fever.

It should be noted that absorption time of rectal preparation of acetaminophen is slower compared to the orally administered route. Rectal absorption of acetaminophen depends on the size, basic component and the solubility of the suppository, its location in the rectum and the ingredients within the rectum (10). It seems that slower absorption of rectal acetaminophen and inability to reach the therapeutic plasma level during the first hour after treatment with the two different doses can be a probable reason for the fact that during the first hour of rectal acetaminophen administration, there is no significant difference between low and high dose preparations. Besides, as the effects of acetaminophen begins to appear 0.5 to 1 hour after treatment and

reaches the peak serum level during 1 to 3 hours (20), detection of the difference between high versus low doses 3 hours after administration in our study seems logical. However, the results of some studies in this regard were not consistent with ours. For example, Nabulsi et al. (21) in a randomized clinical trial on 51 children compared the antipyretic effects of two doses of 35mg/kg and 15mg/kg of rectal acetaminophen and an oral dose of 15 mg/kg. Results of this study revealed no significant difference in maximum antipyretic effects of the drug, needed time for 1°C reduction of body temperature and mean body temperature among the three groups of patients. Based on the results of this study, antipyretic effects of the standard dose of oral and rectal acetaminophen and the higher dose of rectal acetaminophen were the same. This finding was in contrary to our results; however, as there were relatively few patients in each of the three groups of this study, the results may have been influenced.

Study limitations: It is possible that the acetaminophen was not distributed equally in the suppository form. Therefore, dividing the suppository into two or four pieces may have not achieved the therapeutic dose of the drug. Furthermore, differences in demographic features of the patients who enrolled in our study, their different underlying diseases, receiving other treatments especially consumption of oral antibiotics prior to the study may be the other factors which have affected the results of the study.

Conclusion: From gathering all these data, it can be concluded that in febrile children, administration of 30 mg/kg of rectal acetaminophen may be more effective than the standard dose in reducing fever after 3 hours of medication without any complication and therefore, this higher dose of rectal acetaminophen can be used to treat fever in children. However, it is necessary to explain the frequent high doses of acetaminophen (> 90 mg/kg/day as mentioned in the introduction) are not recommended because it increases the chances of associated complications. Therefore, we propose this high dose rectal acetaminophen as initial (loading) dose in the treatment of febrile children.

Acknowledgements

There is no acknowledgments.

Authors' Contribution

Study concept and design: Hashemian, and Momtazbakhsh. Analysis and interpretation of data: Hashemian, Momtazbakhsh, and atrkar Roshan. Drafting of the manuscript: Hashemian. Critical revision of the manuscript for important intellectual content: Hashemian, Momtazbakhsh, and atrkar Roshan. Statistical analysis: Hashem-

ian, and atrkar Roshan.

Financial Disclosure

This study was done by the researchers' autonomous investment.

Funding/Support

Non declared.

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