

ANTIPYRETIC EFFECT OF ORAL VERSUS RECTAL ACETAMINOPHEN IN CHILDREN - A RANDOMIZED COMPARATIVE STUDY

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ABSTRACT

Objective: Acetaminophen is one of the widely used analgesics & antipyretics around the world. Because of its safety, it is widely used in children for the relief of fever. It is available in both oral(solid, liquid) & rectal forms(Suppositories). Different studies shown their efficacy in reducing pain & fever, however the results varies due to absorption, distribution, metabolism and excretion. **Methods:** This randomized control trail studies were conducted in the Dr. M R Shishu Hospital. Then the data were entered into the computer and calculated the result using SPSS. **Results:** In the study it has been found that the mean temperature of the oral group ((37.6⁰C) is quite similar to the mean temperature of the rectal group (37.8⁰C). By the end of the study (180

minutes), 76.9% (n = 60) children experienced a temperature drop that was either equal to or more than 1⁰ C. When the data was stratified by the study groups, the respective proportions in the oral and in the rectal group were found to be 75% (n = 30) and 78.9% (n=30). Likewise, by The end of the study (180 minutes), a total of 44.8% (n = 44) children experienced a temperature drop that was either equal to or more than 2⁰c. When the data was stratified by the study groups, the respective proportions observed in the oral and in the rectal group was 37.5% (n = 15) and 52.6% (n=20). By the end of the study was statistically no different between the oral and the rectal group. **Conclusion:** Oral and rectal acetaminophen preparations seems to be equally efficacious for the treatment of fever and pain. Our randomized controlled trial tested the difference between the two forms of administration at a standard dose and found that the groups did not differ on any of the three outcomes: mean 3-

hour temperature change, percent of patients with a decrease $\geq 1^{\circ}\text{C}$, and percent of patients with a decrease $\geq 2^{\circ}\text{C}$. Therefore, we concluded that there is no significant difference in reducing fever through rectal and oral dosage form, both seems to be very efficacious.

KEYWORDS: Acetaminophen, Fever, Pediatrics, Oral Paracetamol and Rectal Paracetamol.

INTRODUCTION

Acetaminophen is one of the most widely used analgesics and anti-pyretic around the world.^[1] Because of its safety, acetaminophen is the most common drug used in children for the relief of fever and pain.^[2,3] It is available in both oral (tablet & liquid) and rectal forms (suppositories). Various research studies have indicated that both forms have potential efficacy for the treatment of fever in children; however, there may be variations in administration, absorption and toxicity.^[4-6] The oral form is the more common and acceptable form of administration among physicians. The rectal forms are often essential for treating febrile children with emesis and in other conditions where oral administration is contraindicated.

There have been several studies conducted during the last two decades that have investigated the appropriate dosage for acetaminophen in children as well as the efficacy for each form of administration.^[7-10] According to the North American clinical textbooks,^[11-14] the recommended weight-based dosing for oral acetaminophen in children is 10 mg to 15 mg/kg every 4 to 6 hours with a maximum of 5 doses per 24-hour period. Weight-based rectal suppository dosing for children is higher at 15-20 mg/kg per dose. Although some investigators both in Europe and North America have tested doses as high as 60mg/kg; there was not a significant difference in the mean temperature change between higher doses and the recommended dose.^[15,16]

The early studies on the antipyretic effect of rectal acetaminophen have shown varying results.^[7,17,19] Some studies suggest that rectal administration may be as efficacious as the oral administration. In addition, there has been variance across studies regarding the drug interval, the time to peak level and the time to reach a therapeutic level.^[20,21] The literature suggests that it may take two additional hours to peak when administered rectally.

As mentioned previously, under certain circumstances rectal suppositories are essential for fever reduction in children. Although, it has been cited in the literature^[4] that the American

Academy of Pediatrics (AAP) has discouraged the use of rectal acetaminophen because of concerns about the toxic effects as well as erratic absorption of the drug; this was not the recommendation for the use of rectal acetaminophen. The AAP did, in fact, publish that certain factors create the potential for inadequate therapeutic effect such as poor absorption and a cumulative toxic effect from excessive or too frequently repeated doses but the recommendation clearly stated that, for parents, rectal acetaminophen therapy should be avoided unless specifically discussed with the health care provider.^[22] There was not a recommendation for discontinuing the use of rectal suppositories in hospitals or by physicians. The reason that parents need specific instructions is because the absorption of the acetaminophen varies depending on where in the rectum it is placed. When the suppository is placed in the distal rectum the drug by passes the liver, whereas with more proximal placement (oral), the drug will go through the first pass of the portal system that is drugs are metabolized in a single passage through the gut wall and liver, which reduces the bioavailability of the drug.^[18]

In the light of the mixed results and recommendations regarding the efficacy of oral and rectal form of acetaminophen, we propose a randomized controlled trial that will test the antipyretic effect of each form using the standard recommended dose. The study was conducted for the first time in Bangladeshi children.

MATERIALS AND METHODS

Types of Study

The study was a randomized controlled trial designed to test the effectiveness of oral and rectal paracetamol in reducing fever in Bangladeshi children.

Place of Study

The study was conducted at DR. M R Khan Shishu Hospital & Institute of Child Health, Mirpur, Dhaka.

Duration of the study: June 1, 2014 and November 30, 2014.

Sample Size

Our clinical experience suggests that oral paracetamol reduces fever in about 60% patients. If we assume that rectal paracetamol is more effective in reducing temperature, and becomes effective in 90% patients, at 95% significance level and 90 degree of freedom, The sample size is calculated as follows:

$$N = \frac{p_1 \times (100 - p_1) + p_2 \times (100 - p_2)}{(p_1 - p_2)^2} \times f(\alpha, \beta)$$

Where $f(\alpha, \beta)$ is a function of α and β , the values of which are taken from table as 10.5 (α , set at 0.05 i.e., 5% significance level and $1 - \beta$ set at 0.90, i.e., 90 degree of power)

Calculating from this formula, in each group 38.4 patients are needed; therefore, 40 patients were included in each group.

Total 80 children who were admitted into the hospital during that time were included in the study. Out of the 40 patients in the rectal paracetamol group, two patients left the hospital signing the risk bond (DORB) before completing the study. They were not included in the final analysis. Therefore, the total sample was 78 (38 = group B). A total of 80 children randomly assigned to either Group A (oral paracetamol) or Group B (rectal paracetamol). A simple randomization procedure was followed by using a lottery method. 80 cards were prepared with random numbers of A and B (40 for each group). After enrollment into the study, one of the cards was picked and the patient was assigned to group A or B accordingly.

Study Procedures: After the patients were assigned to one of the two treatment groups, the medicine was administered as follows. For group A, commercially available oral paracetamol was given in a dosage of 15 mg/kg. Group B, on the other hand, was given in the range of 15 mg/kg rounded up to 60, 125 or 250mg, of lipophilic paracetamol also available commercially, but used in a suppository form. When needed by the dosing requirement to cut the suppository, after appropriate lubrication, the study worker inserted the suppositories beyond the internal sphincter of the rectum. It was ascertained by sudden release of pressure. Temperature was first assessed before the paracetamol was given using an electronic thermometer calibrated according to international standard and recorded properly. After the drug was administered, either orally or rectally, temperature was again measured at 10, 30, 60, 90 and 180 minutes using the same thermometer. All the patients were followed up for at least 180 minutes.

Research Approach

General: To compare the onset of defervescence of fever with oral and rectal paracetamol in children.

Specific

- Rate of decrement of fever in oral and rectal paracetamol.
- Sex and age variation in the decrement of temperature.
- Three hours temperature change in oral and rectal paracetamol.

Data Analysis

Continuous variables such as age of the children at study entry and temperature readings at different study time points were examined for outlier values, which were then verified against the raw data and found to be correctly coded. The continuous variables were also plotted to assess normality. The coding of the categorical variables (for example gender) was checked and contingency tables were created.

First, we compared the study groups (Oral vs. Rectal Acetaminophen) by baseline characteristics to assess whether randomization worked. Age and sex of the study participants as well as their body temperature at the study entry were used for that purpose. Two-sample t-test was used to compare the age and the baseline body temperature while Chi-square test was used to compare the gender distribution.^[30]

Once the randomization was checked, we moved on to test the specific study hypotheses. To test the first hypothesis, we first plotted the mean temperature between the two study groups (Oral vs. Rectal Acetaminophen) over the study time points (0, 10, 30, 60, 90, and 180 minutes). From the plot we assessed the rate of temperature change between the study groups at different time periods. We then formally tested our first hypothesis of no difference in the temperature at the end of study period (180 minutes) by means of two-sample unpaired t-test.

In the next step, we calculated the proportion of children who experienced a temperature drop of $\geq 1^{\circ}\text{C}$ by the end of the study (180 minutes); this was done in the whole sample and in each study group. We then assessed our second hypothesis of no difference in the proportions of children between study groups who experienced by the end of the study a temperature drop of $\geq 1^{\circ}\text{C}$. Chi-square test was employed to test the hypothesis.

Finally, we also calculated the proportion of children who experienced a temperature drop of $\geq 2^{\circ}\text{C}$ by the end of the study (180 minutes), this was done in the whole sample and in each study group. We then assessed our last hypothesis of no difference in the proportions of

children between study groups who experienced by the end of the study a temperature drop of $\geq 2^{\circ}$. Chi-square test was employed to test the hypothesis.

All tests employed in the study were two-sided; the level set for the tests was 0.05. SPSS was used to carry out the analysis in the computer.

RESULTS

Age Distribution of the Children: The study sample included 78 children who were between 1 and 5 years at study entry. The mean age of the sample was 17 months and the associated standard deviation (SD) was 6.1. When stratified by the study groups, the mean age (in months) and the corresponding SD for the oral and the rectal acetaminophen group were found respectively as follows: 16.0 ± 5.1 and 18.0 ± 8.1 (**Table 1**). The two-sample unpaired t-tests was used to compare the mean age of the two groups that produced a test statistic of 1.35 with 76 degrees of freedom ($n + n - 2$; $40 + 38 - 2 = 76$); the corresponding p-value of the test statistic was found to be 0.19. As a result, we concluded that the mean age of the two groups were not statistically different from each other at the 5% significance level.

Table 1: Comparison of Age between the study groups (Oral vs. Rectal) at study entry

	Acetaminophen study participants (total =78)		
	Oral (n = 40)	Rectal (n = 38)	
Variable	Mean \pm SD	Mean \pm SD	p-value
Age (in months)	16.0 ± 5.1	18.0 ± 8.1	0.19

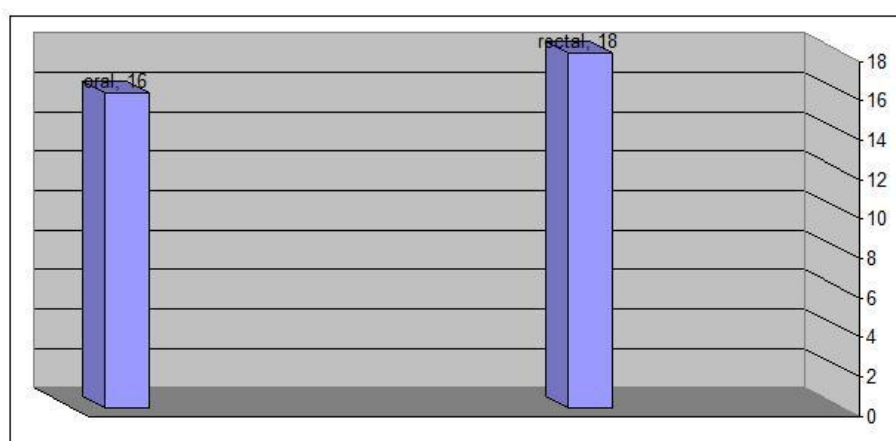


Fig. 1: Comparisons of age between two groups.

Gender Distribution: In the sample, the frequency of male children ($n = 46$, 58.9%) were higher than the frequency of female children ($n = 32$, 41.1%). Of the 46 male children enrolled into the study, 50% were ($n = 23$) in the oral groups and the remaining 50% were in

the rectal group. Of the 32 female children enrolled, the corresponding frequency in the oral and the rectal group were 53% (n = 17) and 47% (n=15) respectively.

Of all the children enrolled in the oral group (n = 40), 57.5% were male; the corresponding frequency in the rectal group (n =38) was 60.5%. Similarly, the proportion of female children in the oral and in the rectal group were 42.5% and 39.5% respectively (**Table 2**). The Chi-square test was used to compare the gender distribution across the study groups, which produced a test statistic of 1.93; the corresponding p-value was 0.10. We accepted the null hypothesis of equal proportions at the 5% significance level and concluded that the male and the female have comparable distribution across the study groups.

Table 2: Comparison of sex between the study groups (Oral vs. Rectal) at study entry

	Acetaminophen study participants (total =78)		
	Oral (n = 40)	Rectal (n = 38)	
Variable	Frequency	Frequency	p-value
Male (n = 46)	57.5%	60.5%	0.10
Female (n = 32)	42.5%	39.5%	

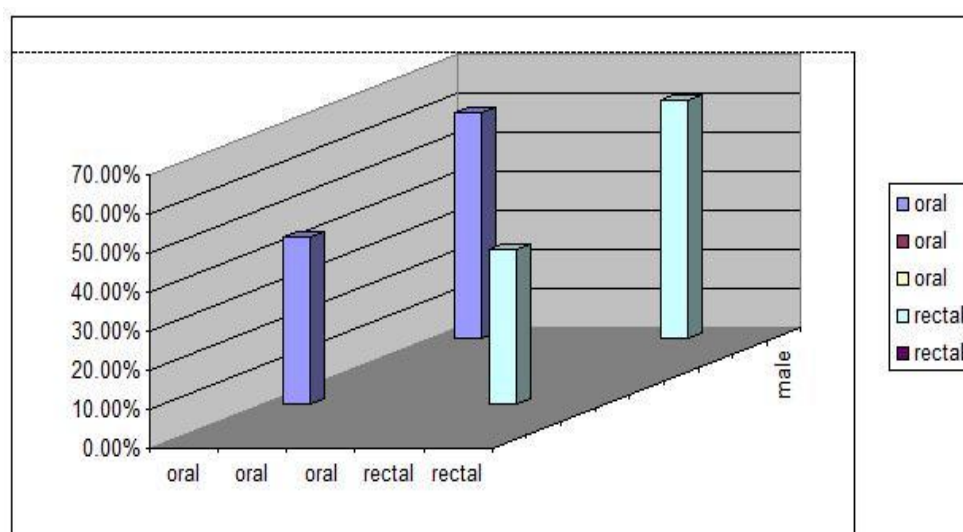


Fig. 2: Sex distribution between two groups.

Baseline Temperature: At the beginning of the study (0 minute) and before the administration of treatment, the mean body temperature in the oral group was 39.6 °C and its corresponding SD was 0.6°C. At the same point of time (0 minute), the mean body temperature and its associated SD for the rectal group were 39.8 °C and 0.8°C respectively (**Figure 2**).

The two-sample unpaired t-test used to compare the mean temperature of the two groups produced a test statistic of 1.24 with 76 degrees of freedom ($n + n - 2$; $40 + 38 - 2 = 76$); the corresponding p-value of the test statistic was found to be 0.90. We concluded that the mean temperature of the two study groups were not statistically different from each other at the 5% significance level.

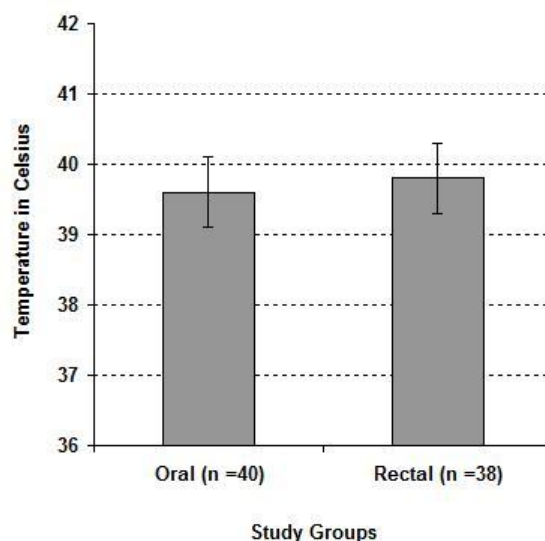


Figure 2: Comparison of baseline temperature (°) between the study groups (Oral vs. Rectal).

Primary outcome: 3-hour temperature change: Figure 3 showed that the mean temperature did not change in the oral group. 10 minutes after the administration of drug. However, the mean temperature decreased an average of 0.4°C in the rectal group during the same time period. Between 10 and 30 minutes into the study, the average temperature drop in the oral group was 0.8°C ; during the same time period temperature decreased on an average of 0.2°C in the rectal group. The highest temperature drop observed in the study was, however, in the rectal group (1.2°C) between 30 and 60 minutes into the study; the corresponding decrease in the oral group during the same time-period was only 0.4°C . Because of that, the total average temperature drop from the beginning (0 minute) to the end of 60 minutes was higher in the rectal group (1.8°C) than it was in the oral group (1.2°C).

On the other hand, the temperature decreased at a higher rate in the oral group than the corresponding decrease in the rectal group from 60 minutes onward (**Figure 3**). For example, between 60 and 90 minutes into the study, the average temperature decrease in the oral group was 0.4°C as opposed to 0.2°C in the rectal group. A further 0.4°C temperature drop was

observed in the oral group between 90 and 180 minutes in the study. During the same time period, no change in temperature was observed in the rectal group (**Figure 3**).

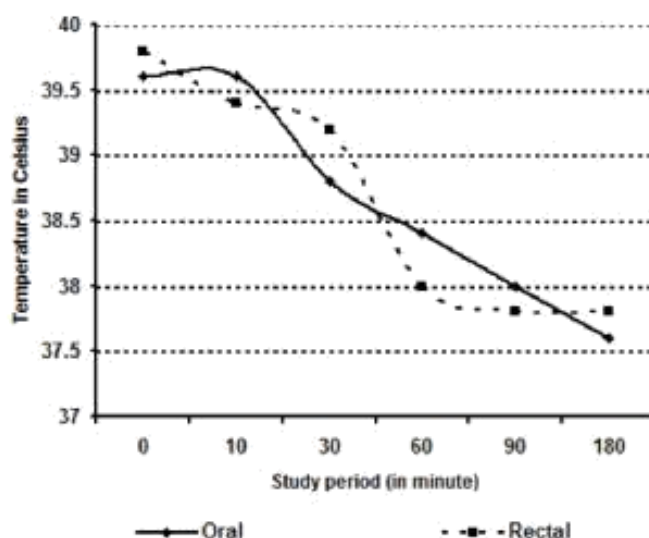


Figure 3: Temperature during the study period: stratified by study groups (Oral vs. Rectal).

Although the pattern of temperature drop was different between the study groups during the various observation time points (**Figure 3**), by the end of the study (180 minutes), the mean temperature in the oral group (37.6°C) was quite similar to the mean temperature of the rectal group (37.8°C) (**Table 3**). The two-sample unpaired t-tests was used to compare the mean temperature between the two groups, which produced a test statistic of 1.72 with 76 degrees of freedom ($n + n - 2$; $40 + 38 - 2 = 76$); the corresponding p-value of the test statistic was found to be 0.08. We accepted the null hypothesis of no difference of temperature between the study groups and concluded that by the end of the study, the mean temperature observed in the oral group was statistically no different from the mean temperature observed in the rectal group.

Table 3: Mean temperature ($^{\circ}\text{C}$) by the study groups (Oral vs. Rectal) at the end of the study period (180 minutes).

Acetaminophen study participants (total =78)			
	Oral (n = 40)	Rectal (n = 38)	
Variable	Mean \pm SD	Mean \pm SD	p-value
Temperature at the end of the study	37.6 ± 0.4	37.8 ± 0.6	0.08

Decrease $\geq 1^{\circ}\text{C}$ in both groups of patients: By the end of the study (180 minutes), 76.9% ($n = 60$) children experienced a temperature drop that was either equal to or more than 1°C . When the data was stratified by the study groups, the respective proportions in the oral and in the rectal group were found to be 75% ($n = 30$) and 78.9% ($n=30$) (**Table 4**). The computed Chi-square test statistic was 0.039; its associated p-value was 0.84. Hence, we accepted the null hypothesis of equal proportions at the 5% significance level and concluded that the proportion of children who experienced $\geq 1^{\circ}\text{C}$ of temperature drop by the end of the study was statistically no different between the oral and the rectal group.

Table 4: Decrease in temperature ($\geq 1^{\circ}\text{C}$) by the study groups (Oral vs. Rectal) at the end of the study period (180 minutes).

	Acetaminophen study participants (total =78)		
	Oral (n = 40)	Rectal (n = 38)	
Variable	Percent (95% CI)	Percent (95% CI)	p-value
Number of patients with a temperature drop of $\geq 1^{\circ}\text{C}$	75.0% (50.8% -89.7%)	78.9% (64.5% - 91.5%)	0.84

Decrease $\geq 2^{\circ}\text{C}$ in both groups of patients: Likewise, by the end of the study (180 minutes), a total of 44.8% ($n = 44$) children experienced a temperature drop that was either equal to or more than 2°C . When the data was stratified by the study groups, the respective proportions observed in the oral and in the rectal group was 37.5% ($n = 15$) and 52.6% ($n=20$) (**Table 5**). The computed Chi-square test statistic was 0.98; its associated p-value was 0.32. Hence, we accepted the null hypothesis of equal proportions at the 5% significance level and concluded that the proportion of children who experienced $\geq 2^{\circ}\text{C}$ of temperature drop by the end of the study was statistically no different between the oral and the rectal group.

Table 5: Decrease of temperature ($\geq 2^{\circ}\text{C}$) by the study groups (Oral vs. Rectal) at the end of the study period (180 minutes).

	Acetaminophen study participants (total =78)		
	Oral (n = 40)	Rectal (n = 38)	
Variable	Percent (95% CI)	Percent (95% CI)	p-value
Number of patients with a temperature drop of $\geq 2^{\circ}\text{C}$	37.5% (29.4% - 44.6%)	52.6% (30.8% -75.2%)	0.32

DISCUSSION

According to our study, it has shown that there is no significant differences to reduce temperature for both oral and rectal administrative forms of paracetamol. To be more specific

we found three strategies that include mean 3-hour temperature change, percent of patients with a decrease $\geq 1^{\circ}\text{C}$, and percent of patients with a decrease $\geq 2^{\circ}\text{C}$. Although paracetamol is randomly used in different parts of the world against elevated temperature and pain. As far as we concern different dosage forms are being prescribed according to patient's compliance. Sometimes, patients are unable for oral administration of paracetamol due to continuous vomiting or other GIT problems. In that case, different administrative forms of paracetamol are introduced in market. Even though absorption is a great concern that may vary different route of administration, there is no other causes related to efficacy or potency for paracetamol administration into human body mainly between oral and rectal route of administration. To recapitulate in the discussion, it could be tell that, both form of paracetamol (oral and rectal) are highly effective to reduce temperature in fever and both of them are equal by means of efficacy and potency.

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