

Comparison of Oral Versus Normal and High-Dose Rectal Paracetamol in the Treatment of Fever in Children

Bastola RC¹, Shrestha SK², Bastola BS³, Shrestha D⁴, Sharma YR⁵

Abstract

Introduction: Paracetamol is the most commonly used drug in paediatrics with the standard dose (15 mg/kg) of oral and rectal paracetamol preparations interchangeably is used to treat fever in children, assuming they have equal antipyretic effect. We did a study to compare the effectiveness of two different rectal doses of paracetamol: 15 mg/kg and 30 mg/kg to that of a standard oral dose of 15 mg/kg. **Material and Methods:** This is a prospective, interventional, randomized controlled study done in Western Regional Hospital, Nepal in which 192 children with fever aged six months to six years. Study duration was August 2015 to October 2015. The sample included 63 in the oral normal dose group (15mg/kg), 59 in normal dose rectal group (15mg/kg) and 70 in high dose (30mg/kg) rectal paracetamol group. Temperature was recorded before and after the administration of paracetamol at an interval of 30, 60, 120, and 180 minutes by using a digital thermometer. **Results:** Total of 59 patients received 15 mg/kg rectal Paracetamol (group A), 70 received 30 mg/kg rectal Paracetamol (group B), and 63 received 15 mg/kg oral Paracetamol (group C). Mean temperature before giving medication in Group A, B and C respectively were 101.7^o F, 101.9^o F and 101.5^o F. At 30 min temperature was 100.8^o F, 100.8^o F and 100.66^o F, while at 60 minutes temperature was 99.9^o F, 99.7^o F, and 99.7^o F respectively for Group A,B and C. But at 120 and 180 minutes temperature decreased significantly who got rectal 30 mg/kg of paracetamol. **Conclusions:** Rectal paracetamol in a dose of 30mg/kg is more effective than oral paracetamol in a dose of 15 mg/kg. However oral paracetamol given in a dose of 15 mg/kg is more effective than rectal paracetamol in a same dose.

Key words: Paracetamol, Oral route, rectal route, temperature, Normal dose, High dose.

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Introduction

People often conceive fever as a disease that requires treatment, rather than being a symptom or a sign of an illness. In their anxious quest to treat fever, parents suffering from "fever phobia" may end up unintentionally overdosing their children with different antipyretics, or with different preparations of the same antipyretics. Paracetamol is the most commonly used drug in paediatrics¹. For

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routine clinical use, it is administered in oral and rectal forms, as a tablet, liquid, or suppository. The rectal route is especially useful in several specific circumstances like vomiting or unconsciousness. Rectal administration of liquid preparations is impractical and has very limited clinical applicability; thus, rectal suppositories occupy an important role in the treatment of fever and pain in children.

Parents, as well as physicians, use the standard dose (10–20 mg/kg) of oral and rectal Paracetamol preparations interchangeably to treat fever in children, assuming they have equal antipyretic effects. However, the evidence for rapid absorption (within 30–60 minutes) and the pharmacokinetics of a single oral dose is well-established^{2,3}. The absorption of rectal paracetamol is erratic and prolonged, varying with the suppository size, composition of its base, rate of dissolution, position in the rectum, and the rectal contents⁴. Moreover, an increasing body of evidence indicates that the rectal Paracetamol dose of 10–15 mg/kg fails to achieve antipyretic serum levels of 10–20 µg/ml. Indeed, a rectal Paracetamol dose of 30–45 mg/kg is needed to achieve adequate serum levels^{5,6}. The recommendation from the American Academy of Pediatrics⁷ has discouraged the use of rectal Paracetamol by parents unless specific instructions are given by medical personnel, their rationale being that there is “potential for inadequate therapeutic effect from poor absorption as well as cumulative toxic effects from excessive or too frequent rectal doses.”

In America, the recommended dose for Paracetamol is 10 to 15 mg/kg/dose every 4 to 6 hours, regardless of the route of administration⁸. Although some investigators^{2,3,6} both in Europe and in North America, have studied and recommended rectal doses as high as 60 mg/kg/dose, these higher doses have not been adopted as standard practice in America and Canada. In one study oral paracetamol proved superior to the rectal preparation⁹, two others^{10,11} saw no difference in the antipyretic responses of oral and rectal paracetamol. However, Vernon's study was un-blinded and lacked placebo control, and compared the standard doses of 15–20 mg/kg of oral and rectal Paracetamol only. Scolnik's study, also lacking blinding and placebo control, was further limited by the fact that it assessed antipyretics during the first three hours after drug administration, a time during which maximum antipyretic effect of rectal Paracetamol may not have occurred.

The objectives of this study were to compare the antipyretic effective of two different rectal doses of Paracetamol: 15 mg/kg and 30 mg/kg to that of a standard oral dose of 15 mg/kg. The individualized doze was given three hours of observation to allow detection

of late antipyretic effect that may occur with rectal Paracetamol. The results of this study could provide further evidence on the comparative antipyretic effects of different doses of rectal Paracetamol versus the standard oral one.

Material and Methods

This was a prospective, interventional, randomized, controlled study done in Western Regional Hospital, Nepal. All febrile children aged six months to six years were included in the study from August 2015 to October 2015. A total of 192 children were included in this study. There were 63 patients in the oral normal dose paracetamol group (15mg/kg), 59 patients in the normal dose rectal paracetamol group (15mg/kg) and 70 patients in the high dose (30mg/kg) rectal paracetamol group.

Fever was defined as Temperature $\geq 38^{\circ}\text{C}$ or 100.4°F . Normal dose oral paracetamol was defined as 15mg/kg/dose, Normal dose rectal paracetamol as 15mg/kg/dose and High dose rectal paracetamol as 30mg/kg/dose.

Patients were assigned to either of the three treatment groups by the use of a computer-generated random-number table. The three treatment groups were as follows: Group A-rectal paracetamol 15 mg/kg in suppository form; Group B- rectal paracetamol 30 mg/kg in suppository form; and group C-oral paracetamol 15 mg/kg in suspension. The suppository was inserted beyond the internal sphincter after appropriate lubrication.

Inclusion criteria involved all children aged six months to six years with axillary temperature $\geq 38^{\circ}\text{C}$ ($\geq 100.4^{\circ}\text{F}$), attending in emergency department or admitted patients with fever in paediatric department of Western Regional Hospital, Pokhara, Nepal. *Exclusion Criteria* comprised of all patient with known allergy to paracetamol, patients with febrile neutropenia, patients who were kept NPO, with the history of vomiting or diarrhoea in the previous four hours, failure of the parents to provide informed consent, patients receiving paracetamol in the previous four hours and the patients who vomited the oral preparation within 20 minutes. Informed written consent from the parents or care taker were taken in a well understood Nepali Language.

Temperatures were recorded before and after the administration of paracetamol at an interval of 30, 60, 120, and 180 minutes by using a digital thermometer (Dr. Morepen). Parents were advised to reduce the amount and thickness of clothing the child was wearing. Axilla was dried with a cloth and bulb of thermometer was

placed snugly by tightly holding the arm against chest. Thermometer was placed in the axilla for two minutes.

The groups were compared using analysis of variance for change in temperature during three hours. Differences in the proportion in each group that experienced a drop of 1°C or 2°C were assessed by ANOVA with Bonferroni Post Hoc comparison, chi square test, chi square (exact) test using SPSS 16.

Results

Fifty-nine patients received 15 mg/kg rectal Paracetamol (group A), 70 received 30 mg/kg rectal Paracetamol (group B), and 63 received 15 mg/kg oral Paracetamol (group C). Among them 26(44.1%) were female and 33(55.9%) were male in Group A. Similarly, in Group B, 29(41.4%) were female and 41(58.6%) were male. In Group C, 24(38.1%) were female and 39(61.6%) were male. Total female children were 79(41.1%) and male, 113(58.9%). All patients under study whether in group A, group B, or group C were enthusiastic and cooperative.

There were no significant differences in age, weight, temperature at 0 min, heart rate and respiratory rate among the three groups as shown in Table-1. Mean of Vitals like heart rate and respiratory rate were also not significant among those three groups and is shown in Table-1.

Duration of fever of different patients from different group were from one day to maximum 90 days (Figure 1). Among total patients 17.2% had history of fever for one day, 36.5% had history of fever for two days. Similarly 20.3% had a history of fever for three days,

4.2% had four days, 5.7% had five days, 1.6% had six days, 5.7% had seven days, 2.6% had eight days, 0.5% had nine days, 2.1% had ten days, 1% had eleven days, 1.6 had thirty days, 0.5% had forty five days and 0.5% had ninety days history of fever.

The maximum drop in temperature for each of the three groups is summarized in Table 2. There were no significant decrease in temperature in all three groups at 30 minutes and 60 minutes but fever decreased significantly at 120 minutes and 180 minutes (Table 2).

At 30 min in Group A mean temperature was 100.8° F, in Group B it was 100.8° F and in Group C it was 100.66° F. This decrement was statistically not significant (p=0.569).

At 60 minutes in Group A temperature decreased to 99.9° F, in Group B temperature decreased to 99.7° F, and in Group C mean decrease in temperature was up to 99.7 ° F. This decrement was also not statistically significant (p=0.261).

But at 120 minutes rectal 15 and 30 mg/kg differed significantly (p=0.01). Other differences being not significant. Similarly, at 180 minutes rectal 15 and 30 mg/kg differed significantly (p=0.005), other differences being not significant.

Since it is possible that temperatures dropped more rapidly in one particular patient or group and this would not be reflected in the calculations described so far, the area under the curve for temperature versus time (Fig 2) was individually calculated for all patients in the three groups. This comparison reveals significance among the three groups at 120 minutes and 180 minutes.

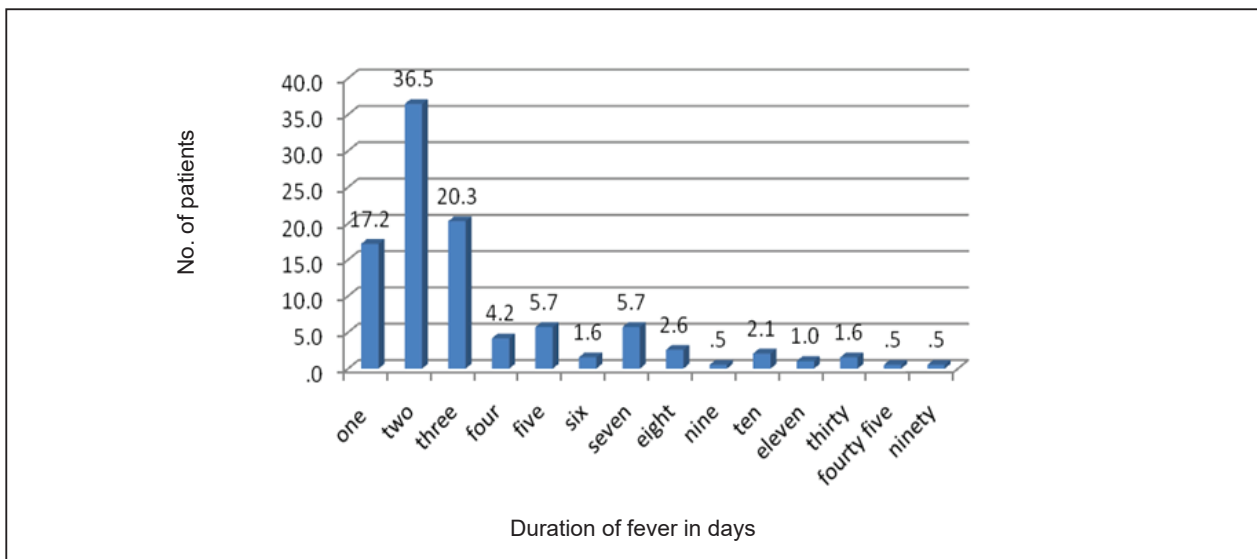


Fig 1: Showing durations of fever among all group patients

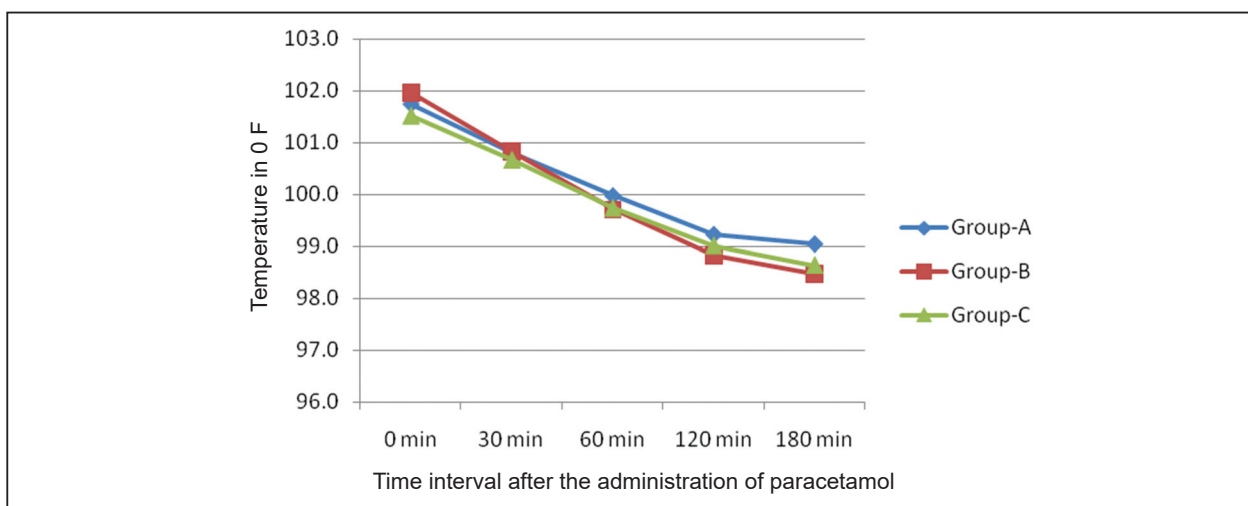


Fig 2: Showing average temperature in °F at each time point for the 3 groups

Table 1: Showing mean for different variables among 3 groups and their p-value

Route and Dose	Rectal 15mg/kg(A)		Rectal 30mg/kg(B)		Oral 15mg/kg(C)		p-value
	Mean (n =59)	SD	Mean (n= 70)	SD	Mean (n= 63)	SD	
Age in month	31.88	20.548	26.23	17.451	25.51	16.469	0.108
Weight	10.953	3.3845	10.821	3.3685	10.894	3.7477	0.977
Fever in Days	5.73	12.422	3.86	6.233	3.17	2.339	0.190
Tem in °F at 0 min	101.746	1.0436	101.963	1.0548	101.511	1.0943	0.053
Heart Rate	126.42	15.133	129.67	13.533	127.49	16.745	0.459
Respiratory Rate	34.36	10.743	36.71	13.450	35.43	14.577	0.592

Table 2: Showing decrease in temperature in different interval following administration of paracetamol

Temperature (F°) in min	Rectal 15mg/kg(A) (n= 59)	Rectal 30mg/kg, (B) (n=70)	Oral 15mg/kg (C) (n=63)
0 min	101.746	101.963	101.511
30 min	100.808	100.83	100.66
60 min	99.978	99.701	99.732
120 min	99.236	98.829	99.008
180 min	99.053	98.464	98.633

Table 3: Showing decrease in temperature in different intervals with mean and SD and their p-value

Time	Temperature (°F)						p-value
	Group-A		Group-B		Group-C		
	Mean	SD	Mean	SD	Mean	SD	
0 min	101.75	1.04	101.96	1.05	101.51	1.09	0.053
30 min	100.80	1.10	100.83	0.92	100.66	0.93	0.569
60 min	99.98	1.23	99.70	0.85	99.73	0.97	0.261
120 min*	99.24	1.09	98.83	0.64	99.00	0.69	0.022
180min**	99.05	1.51	98.46	0.65	98.63	0.82	0.006

Discussion

In febrile children, brought to an emergency, OPD and indoor departments of Western Regional Hospital, the single-dose oral paracetamol was more effective than rectal paracetamol 15 mg/kg. But when we doubled

the dose of rectal paracetamol, we found additional benefit over both oral and rectal paracetamol 15mg/kg. Moreover, the rectal route was as satisfactory to the parents as the oral route.

The use of high-dose rectal paracetamol has been studied extensively^{3,9,10}. They suggest that higher doses of rectal paracetamol (30 mg/kg) was more effective in reducing fever than oral and rectal 15mg/kg paracetamol. The study done in Iran in 2010 A.D. by Karbasi et. al.¹² which was prospective parallel group designed study, 60 children who presented to the emergency department or outpatient paediatric clinic at a tertiary hospital and aged from six months to six years with rectal temperature over 39 °C were enrolled. Patients were randomly assigned to two equal-sized groups. Group 1 received 15 mg/kg acetaminophen rectally and group 2 received the same dose orally. Temperature was recorded at baseline and 1 and 3 hours after drug administration. The result showed Rectal and oral paracetamol preparations had equal antipyretic effects in children. The rectal route was proved to be as acceptable as the oral one for the parents.

Rumack¹³, in an unreferenced review, quoted that therapeutic level of paracetamol in serum was 10 to 20 mg/L. Walson et al¹⁴ found that even concentrations of paracetamol as low as 6.8 mg/L reduce temperature to a significantly greater extent than placebo. Others did not find a correlation between maximal serum concentration and fall in temperature¹⁵. The weak correlation between serum concentrations and clinical outcome, and the availability of temperature as a reliable and objective outcome measures were the reasons why we choose to study the effect of different doses and routes of paracetamol without assessing serum levels. This study was however limited as it could not assess the systemic absorption of the drug. Previous studies on the antipyretic effect of rectal paracetamol in children yielded conflicting results. Keinanen et al¹⁶ showed that both oral and rectal paracetamol were effective in reducing temperature in febrile children: the maximal temperature decrement was significantly greater in the oral group, and the effect was seen earlier. However, this study was not randomized. Moreover, a relatively low dose i.e. 10 mg/kg paracetamol was used in the study.

In a nonrandomized trial¹⁴, administering 15 mg/kg paracetamol to the same febrile patients either rectally on the first day after cardiac surgery or via nasogastric tube the next day produced no difference in temperature reduction.

In a randomized study, Vernon et al¹⁷ showed no difference in the decrement in fever among 37 children who were treated with either oral or rectal acetaminophen in a dose of 15 to 20 mg/kg. However, the effect of high-dose rectal paracetamol was not investigated. Treluyer JM et al¹⁸ showed that 30 mg/kg oral paracetamol caused a swifter and greater decrement in fever than conventional doses of 15 mg/kg, with mean difference in temperature was 0.5°C. Our study also showed a similar finding on administering 30mg/kg rectal paracetamol.

Parents were found satisfied equally with the rectal and oral routes of administration of paracetamol but the results would have been difficult if they had inserted the suppository themselves. Thus, rectal route is preferred especially in condition where oral route poses difficulties, such as with the child who is vomiting or spitting up oral medications.

Conclusion

Rectal paracetamol in a dose of 30mg/kg is more effective than oral paracetamol in a dose of 15 mg/kg. However oral paracetamol given in a dose of 15 mg/kg is more effective than rectal paracetamol in a same dose. Thus, rectal paracetamol in a dose of 30 mg/kg is superior to oral route both because of its rapidity of action in bringing down the temperature in a febrile child and of easy administration.

Limitations of Study: This study has several limitations. It was randomized but not blinded or placebo controlled. This was because the primary outcome measure was an objective measure (body temperature), which was not subjected to observer bias and blinding was not considered necessary.

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