A Randomized Controlled Trial of Defervescent Efficacy of Oral versus Rectal Paracetamol in a Pediatric Acute Care Setting

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ABSTRACT

Objective: To assess the comparative efficacy of oral versus rectal paracetamol in reducing fever in a pediatric acute care setting.

Methods: 200 children with body temperature >39ºc were randomized to receive oral or rectal paracetamol, together with tepid sponging. Their body temperatures were measured at enrollment, after fever reduction protocol had been completed and at 30-minute and 60-minute intervals. General linear model was used to assess the effect of time and type of medication on fever reduction.

Results: Mean log [temperature] differed significantly between time intervals ($F(1.275, 248.576) = 32.766$, $p<0.001$) and the test of between subject effects showed that there was a significant effect of antipyretic types on mean body temperature of children at different time intervals ($F(1,995) = 4.040$, $p<0.05$).

Conclusion: Rectal paracetamol was shown to be more effective overall at lowering body temperature, especially at the termination of fever reduction protocol, and at 60 minutes.

Keywords: Paracetamol, fever, rectal suppository, defervescence

Siriraj Med J 2016;68:37-41
E-journal: http://www.sirirajmedj.com/ojs

INTRODUCTION

Fever management is an integral part of pediatric medicine. Last year, approximately 4,000 children presented to the Outpatient Department at Siriraj Hospital whose sole complaint was fever, which accounted for over 10 percent of all acute care visits. Recognizing and treating fever effectively can reduce unwanted complications in the acute care setting. Antipyretic administration, together with tepid sponging, forms the mainstay of fever reduction in the tropics. At the Department of Pediatrics, standardized Fever Reduction Protocol (FRP) has been in practice since 2001 and includes immediate administration of oral paracetamol and tepid sponging for 15 minutes in children under 4 years of age with fever above 38.5ºc. Since its implementation, the number of febrile convulsions occurring in the waiting room has decreased 8 folds.[1] However, administration of oral medication in young children can be time-consuming and inefficient, with 1 in 7 children vomiting up medication within 20 minutes.[2] A more efficient method of rectal administration

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Received 17 July 2015
Revised 11 September 2015
Accepted 29 September 2015

can rectify this problem. However, its pharmacokinetic limitations, particularly a slower, more erratic absorption with significant lag-time to peak serum concentration[3] makes this method of fever reduction unpopular and limits its usefulness in acute care situations. Moreover, the efficacy of rectal formulation when used in conjunction with tepid sponging has never been evaluated. The objective of this study was to compare the efficacy of body temperature reduction of orally versus rectally administered paracetamol, when used as part of the standard fever reduction protocol in a pediatric acute care setting.

MATERIALS AND METHODS

Eligibility criteria: The study was conducted at the walk-in, acute care section of the Outpatient Department at Siriraj Hospital between January to June 2010. Children ages 60 days to 36 months with temperatures of >39ºc, measured via infared tympanic thermometer or rectally at the triage desk were screened. Those with blood pressure <10th percentile for weight, respiratory rate >60 per minute, heart rate of >180 beats per minute, a history of febrile convulsion within the prior 48 hours, received paracetamol less than 4 hours prior to screening, had active diarrheal disease, or a history of paracetamol hypersensivity were excluded. A repeat temperature measurement with an automated digital axillary thermomether (Terumo™) was done prior to enrollment. Those with repeated temperature <39ºc were excluded from enrollment and received routine oral paracetamol and/or tepid sponging as appropriate.

The study protocol was approved by Siriraj Hospital Internal Review Board (Si. 526/2009). The Informed Consent was signed by parents or legal guardians prior to enrollment of subjects.

Allocation of subjects: Enrolled patients were assigned to either oral paracetamol (Standard) group or rectal paracetamol (PoroSuppo) group using block randomization performed ahead of time by the project's Clinical Research Nurse (CRN1), using a block size of 8. The CRN1 placed the random numbers in sealed envelopes, together with the assigned method for fever reduction. After enrollment, parents take the envelope to the tepid sponge area. A second Clinical Research Nurse (CRN2) will ask the parents to leave before administering the assigned medication with the curtains drawn around the bed. Then, a nursing assistant trained to carry out the tepid sponging will enter and complete the rest of the fever reduction protocol (FRP). Re-assessments of body temperature were done an additional 3 times, at termination of FRP (T0), then at 30 (T30) and 60 minutes (T60).The overall patient flow is shown is Fig 1. The same nursing assistant who was blinded to the type of medication which was given carried out all body temperature measurements at T0, T30 and T60. Oral paracetamol was administered to the Standard group at 15 mg/kg/dose, given to the nearest milliliter. The PoroSuppo group received Poro Suppo®, a paracetamol rectal suppository, at 25-30 mg/kg/dose. Poro Suppo® 125 mg suppositories were cut into halves and quarters to achieve the closest dose possible. Patients were also monitored for drug tolerability. Patients who defecated within 15 minutes or vomited within 20 minutes

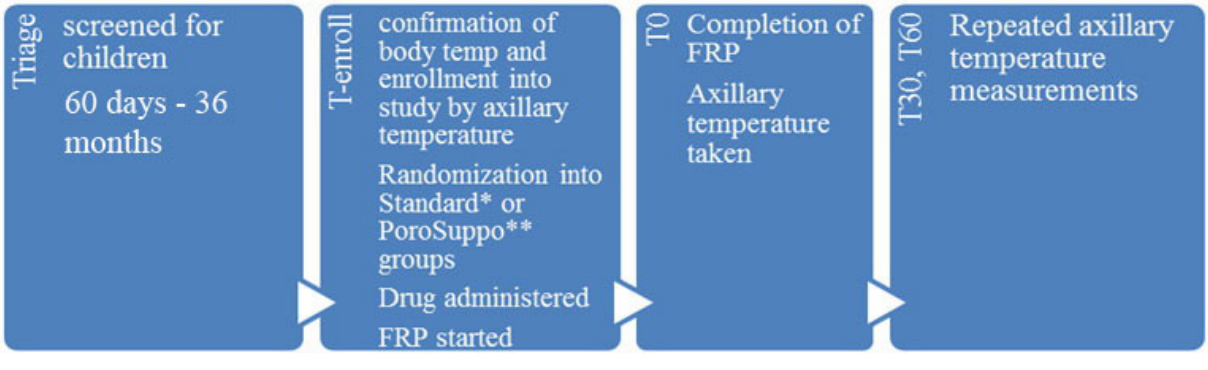

Fig 1. Study design and patient flow diagram.
*Paracetamol 15 mg/kg/dose oral, **Paracetamol suppository 25-30 mg/kg/dose per rectum

were reported to CRN2 and the medication was re-administered.

The primary objective of the study was to compare the rate of temperature reduction between the Standard and the PoroSuppo groups at termination of FRP, and at 30 and 60 minutes. Secondary objectives included comparison of tolerability between the two methods and assessment of the defervescent impact, defined as the ability to achieve body temperature of <38ºc, of each method.

Sample size: Scolnik et al[14] conducted a randomized controlled trial comparing the administration of paracetamol administered rectally (15 mg/kg/dose and 30 mg/kg/dose) to normal oral dose paracetamol. The effect size used in that study was 0.5ºc and the sample size was 30 in each of the 3 groups. For our study, we opted for a smaller effect size of 0.3ºc, alpha of 0.05, standard deviation of 0.74 and ratio of control to experiment patient of 1:1. The calculated sample size was 90 in each group. To allow for dropouts, 100 patients were recruited to each group.

Medication:

The oral paracetamol was manufactured by Greater Pharmacy Organization and the 120 mg per 5 ml. formulation was used throughout the study. The rectal paracetamol used was Poro Suppo® imported by Harn Thai Pharma (2508). The formulation used was the 125 mg rectal suppository.

Data analysis:

For primary outcome, the rate of temperature reduction of the two groups were first plotted to assess normality. The groups were compared using analysis of variance. Log of mean temperatures over time were analyzed using repeated measure ANOVA with one within subject effect (time) and one in-between subjects effect (paracetamol formulation).

RESULTS

A total of 230 patients were screened and 200 were enrolled. Due to early enrollment at Triage Desk, all patients were able to complete their temperature assessment at T60 (Fig 2). Demographic data showed that children enrolled in the Standard group tended to be older. The average body temperature (ºc) at T0 between the Standard vs. PoroSuppo groups were [(37.98+ 0.76) and (37.68 + 1.18), $p<0.05$], respectively (Table 1). Three out of 100 patients in the standard group did not tolerate the drug and needed the drug to be re-administered, compared to none in the PoroSuppo group. There was a greater proportion of patients in the PoroSuppo group who achieved deffervescence at 30 minutes than the Standard group (34% vs. 29%), but the difference was not statistically significant.

A Generalized Linear Model using repeated measures ANOVA with a Greenhouse-Geisser correction determined that mean log[temperature] differed significantly between time intervals ($F(1.275, 248.576) = 32.766$, $p<0.001$), (Fig 3). Also the test of between subject effects showed that there was significant effect of antipyretic formulation on mean body temperature of children at different time intervals ($F(1, 995) = 4.040$, $p<0.05$).

DISCUSSION

Recommended dosing for rectal administration of paracetamol is 25-30 mg/kg/dose, higher

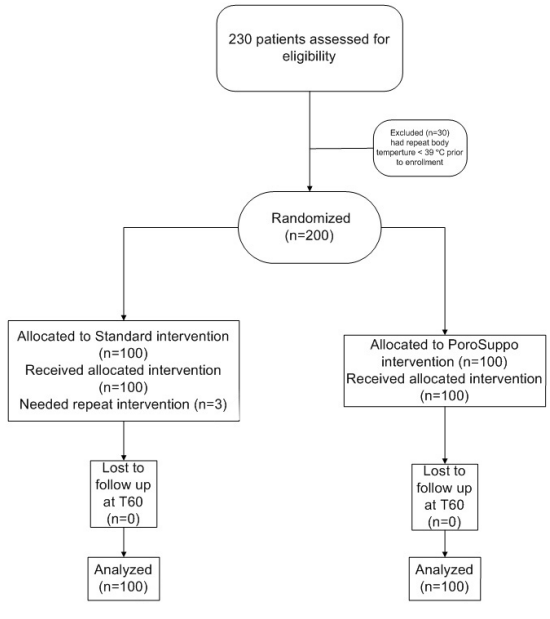

Fig 2. CONSORT diagram for patient enrollment.

TABLE 1. Baseline characteristics and average temperature** at different time interval.

	Oral paracetamol group (Standard) (N = 100)	Rectal paracetamol (PoroSuppo®) (N = 100)	P-value
Male gender (N)	58	51	
Age (years, mean ±S.D.)*	2.14±1.17	1.66±0.88	0.05
T-enroll (°C, mean ±S.D.)	39.25±0.5	39.1±0.53	0.53
T0* (°C, mean ±S.D.)	37.98±0.76	37.68±1.18	0.05
T30 (°C, mean ±S.D.)	38.27±0.64	38.16±0.66	0.66
T60 (°C, mean ±S.D.)	37.97±0.56	38.07±0.63	0.63

T-enroll = temperature at enrollment, T0 = temperature at completion of FRP, T30 = temperature at 30 minutes after FRP, T60 = temperature at 60 minutes after FRP

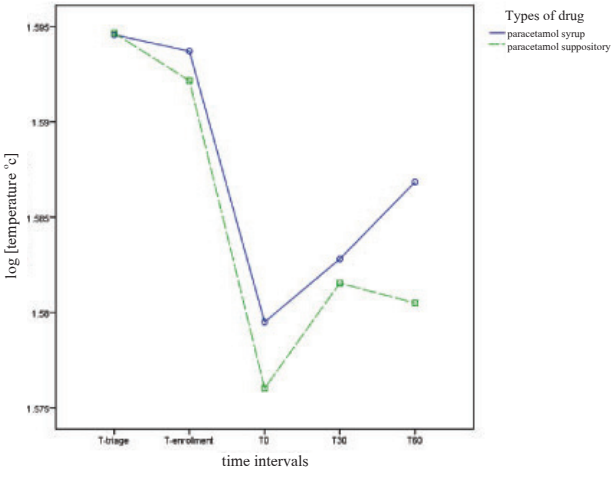

Fig 3. Estimated marginal means of Log [temperature] between PoroSuppo and Standard group.

than that of oral dosing. Although there have been many studies which evaluate the comparative efficacy of oral versus rectal paracetamol in reducing fever, few have evaluated them in combination with tepid sponging in the context of a standardized fever reduction protocol. Tepid sponging is a recommended practice in areas of the world where ambient temperature is high and can impede rate of fever reduction.[4,5] When used in conjunction with paracetamol, randomized controlled trials have consistently clearly shown that tepid sponging will result in greater temperature decrease in the first 30 minutes.[6-8] On the other hand, the form of paracetamol recommended for febrile children under an acute care setting remains controversial. A double-blind, placebo-controlled trial evaluating the antipyretic efficacy of oral paracetamol versus 2 different dosages of rectal paracetamol found no difference among the 3 groups in either time-to-maximum temperature reduction or time-to-temperature reduction of at least 1 degree celcius.[9] A subsequent meta-analysis study also substantiated this conclusion.[10] Yet, in resource-limited areas such as the acute care clinic or emergency department, rectal paracetamol can help to ensure compliance, save time and man-hours as well as provide a viable alternative for temperature reduction.[11-13]

The effect of early temperature reduction achieved with tepid sponging, regardless of paracetamol formulation, was evident in our study. However, rectal paracetamol was still shown to be more effective at lowering body temperature both at the termination of FRP, and at 60 minutes. It is well known that tepid sponging can reduce body temperature rapidly, but its effect is short-lived. In our study, average body temperature of subjects began to rise at the cessation of FRP, although at 30 minutes there was no significant difference between the two groups. However, despite such rebound, the rectal paracetamol group showed more suppressed body temperature over all. In addition, at T60, the standard group showed a clear upward trend in body temperature while the PoroSuppo group exhibited a more sustained defervescence, although this difference was not statistically significant. Finally, in dealing with acutely ill children, rectal paracetamol has an added benefit since it is much better tolerated, needing no re-administration.

The limitation of this study included the fact that, although patients are randomized, there

was still a statistically significant difference between the mean age of the two groups. However, the impact of this on temperature reduction was unclear. In addition, due a small sample size, the impact of rectal paractemol on body temperature at 60 minutes was not evident.

CONCLUSION

In an acute care situation, paracetamol suppository, together with appropriate tepid sponging, can effectively reduce fever and keep body temperature down longer than oral paracetamol.

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