Prospective Clinical Research Report

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
49(3) 1–8

DOI: 10.1177/0300060521999755
journals.sagepub.com/home/imr
SAGE

Randomised comparative trial of the efficacy of paracetamol syrup and dispersible tablets for the treatment of fever in children

Benjamin Okereke[1], Okezie Ibeleme[1] and Adaobi Bisi-Onyemaechi[2]

Abstract

Objective: Fever is the most common reason for the presentation of children in the outpatient department. Paracetamol is marketed in different formulations for ease of administration to the paediatric population. These include syrups, dispersible tablets and rectal inserts. Dispersible tablets disintegrate rapidly in liquid and are subsequently taken orally, providing another oral formulation. We determined if there is a difference in the antipyretic efficacy of the syrup and the dispersible formulation of paracetamol, thereby prompting the development of the latter (another oral formulation) for use in children.

Methods: A randomised, controlled, double-blind intervention of a single dose of both formulations was given to febrile children, and their temperatures were documented twice in 30-minute intervals. Temperature changes were compared statistically.

Results: The mean temperatures at recruitment were $38.2 \pm 0.5^{\circ}C$ and $38.3 \pm 0.6^{\circ}C$ for the dispersible and syrup group, respectively. There was no significant difference between the temperature changes at T2 (30 minutes) and T3 (60 minutes) between the two study arms. However, the temperature was significantly different at T1 (baseline), T2 and T3 within the dispersible and syrup groups.

Conclusion: The decreasing trend in temperature was similar in both groups. Both preparations produced statistically similar antipyretic effects with no reported adverse drug reaction.

[1]College of Medicine, University of Nigeria Ituku-Ozalla Campus, Enugu, Nigeria
[2]Department of Paediatrics, College of Medicine, University of Nigeria Ituku-Ozalla Campus, Enugu Nigeria

Corresponding author:
Adaobi Bisi-Onyemaechi, Department of Paediatrics, College of Medicine, University of Nigeria Ituku-Ozalla Campus, P.M.B 01129. Enugu –Port Harcourt Express way, Enugu 400001, Nigeria.
Email: adaobi.bisi-onyemaechi@unn.edu.ng

Keywords
Paracetamol, antipyretic, syrup, dispersible, fever, paediatric

Date received: 25 January 2021; accepted: 8 February 2021

Introduction

Fever is the most common reason for presentation in the outpatient department for children. It is defined as the regulation of body temperature at an increased level.[1–3] It is usually a symptom of an underlying process and rarely harmful on its own. Fever is defined as a core temperature greater than 37.5°C for clinical and research purposes.[4,5]

The treatment of fever has been a subject of controversy over the past decades.[6–10] However, treatment is advocated to relieve the discomfort associated with fever. Fever can be relieved manually (sponging) and by using pyretic drugs.

Acetaminophen, also known as paracetamol, is an effective drug for the reduction of fever and is typically not associated with side effects. However, the response of fever to paracetamol is not useful to determine the cause of the fever.[11]

Paracetamol is available in different formulations. These include syrups, dispersible tablets and rectal inserts. Dispersible paracetamol is a formulation recently introduced into the market as an alternative to the other forms. Dispersible tablets disintegrate rapidly in liquid and are subsequently taken orally, thereby providing another oral formulation of the medication similar to syrup.

The researchers in this study aimed to compare the antipyretic efficacy of two oral paracetamol formulations (syrup and dispersible) and determine if there is a difference between them. Our findings prompted the development of a second recently introduced dispersible (oral) form of the medication for children. We also monitored any possible side effects of the drugs.

Methods and materials

This was a spontaneous study not promoted by industry. This investigator-blind, randomised, parallel-group, multiple-arm, comparative, single-dose trial was performed at the Paediatrics Department of a secondary health facility in Enugu Metropolis. Ethical approval was obtained from the Health Research Ethical Board of the University of Nigeria Teaching Hospital Ituku-Ozalla Nigeria, and written informed consent was obtained from the caregivers of the study participants prior to enrolment. Enugu is the largest city in South East Nigeria, and this is the largest secondary health facility in the city of Enugu. The study participants included children from different ethnicities in Nigeria because the health facility is located close to the settlement of non-indigenes of the state. The participating children were all from the lower socioeconomic class. The inclusion criteria were children of either sex between 6 months and 12 years of age with a tympanic temperature of greater than 37.5°C.

Patients were excluded if they had received any antipyretic drug in the previous 6 hours, had any severe or life-threatening infections, had a circulatory collapse, active bleeding or organ failure, showed features of immunosuppression or were on any medication that would interfere with the study. Participants were withdrawn if an adverse effect was observed during the study or because of voluntary withdrawal by the guardian or caregiver.

The study participants were randomly distributed into two groups. Group A received a single dose of paracetamol syrup (Emzor Pharmaceuticals, Lagos, Nigeria) at 15 mg/kg, and group B received a single dose of dispersible paracetamol (Sinolax 125; Nemel Pharmaceuticals, Enugu, Nigeria) at 15 mg/kg. The tympanic temperature was measured in intervals of 30 minutes for 1 hour. The calculated minimum sample size was 20 patients in each treatment group, with the power set at 0.8.

Study procedures

The age, sex, weight, treatment received and detailed history of the participating children were documented in a coded case record form. The study participants who fulfilled the inclusion were temporarily admitted. The participants were randomly assigned to groups A or B by the blinded investigator using random computer-generated sequences. After generation of the random sequences, these were written down, placed in a box with a pinhole and handed over to the research assistant/study nurse. The recruited participants were then asked to select a paper. The medication (syrup or dispersible) was given by the nurses depending on what was written on the paper picked by the participant. The baseline temperature (T1) of each participant was subsequently measured by the researchers and handed over to the participant, who gave it back to the study nurse (in a different room) for documentation. In this way, the investigators were blinded to the intervention that each participant was given. The tympanic temperature was measured using a tympanic infra-red thermometer Thermoval@ Duo scan (Hartmann Heidenheim, Germany). The measurement for the ear mode was from 32.0°C to 42.2°C with a measurement accuracy of ± 0.2°C in accordance with European Standard EN 12470-5. Appropriate doses based on weight using 15 mg/kg of the paracetamol syrup and dispersible paracetamol were administered. Drugs were administered as a single oral dose. The dispersible tablets (125 mg) were dissolved in 5 mL of table water for every tablet to simulate the syrup concentration of 120 mg/5 mL. The children (from either study group) who requested water after receiving the medication were given a maximum of 100 mL. The dose of the study drug was repeated for any child who vomited the medication within 30 minutes of the drug administration. The tympanic temperature was recorded in 30 minutes intervals (T2 and T3) for 60 minutes post-intervention. At each point during the study, temperature readings were recorded three times, and an average of the readings was documented.

The primary endpoint for efficacy was the reduction in the tympanic temperature from the baseline temperature to 1 hour after drug administration.

The secondary endpoints were the per cent reduction in temperature from baseline to 30 minutes post-intervention, proportion of afebrile children at 30 minutes post-dose and any adverse drug events during the 1-hour period. The phone numbers of the researchers were given to the study participants in case any adverse event occurred after the study.

Statistical analysis

Data were analysed using IBM SPSS Statistics for Windows, Version 20 (IBM Corp., Armonk, NY, USA) and presented in tables. Comparisons of mean temperatures were performed using a Student's t-test, and comparisons of the proportion of participants with fever were performed using the Chi-square test. The Duncan multiple range comparison test was used to assess whether the difference between the mean temperatures of both study arms was significant. All statistical tests were

two-tailed with significance determined by reference to the 5% level.

Results

The study enrolled 74 participants between September and December 2018. Fifty-two participants eventually completed the study (Figure 1). The majority were within the age range of 1 to 4 years (Table 1). Only one child vomited his medication, which was readministered after 20 minutes. Three patients refused to take their syrups and eventually withdrew from the study. Nine patients did not complete the study because their caregivers had to leave the facility before the study was completed (Figure 1).

The mean baseline temperature of the study participants at recruitment was $38.2 \pm 0.5°C$ in the dispersible arm and $38.3 \pm 0.6°C$ in the syrup group. The mean temperature for each of the study arms at different times during the study is shown in Table 2.

There was no significant difference in temperature at baseline, time T1 and time T2 between the dispersible and syrup drug groups. However, the temperature was significantly different across times T1, T2 and T3 within the dispersible group ($F = 6.018$, $P = 0.004$). Similarly, the temperature was significantly different across times T1, T2 and T3 within the syrup group ($F = 5.018$, $P = 0.009$). The Duncan multiple comparison test indicated that the significant difference found within the groups was not between T1 and T2 but between T1 and T3.

There was no significant difference between the changes in temperature at times T2 and T3 between the two study arms (Table 3).

There were no observed or reported side effects from the medication. At T2, dispersible paracetamol produced a temperature decrease of less than 0.5°C in 70% of the participants in the treatment group. This was similar to the syrup treatment group, in which 64% of the participants showed a temperature decrease of less than 0.5°C.

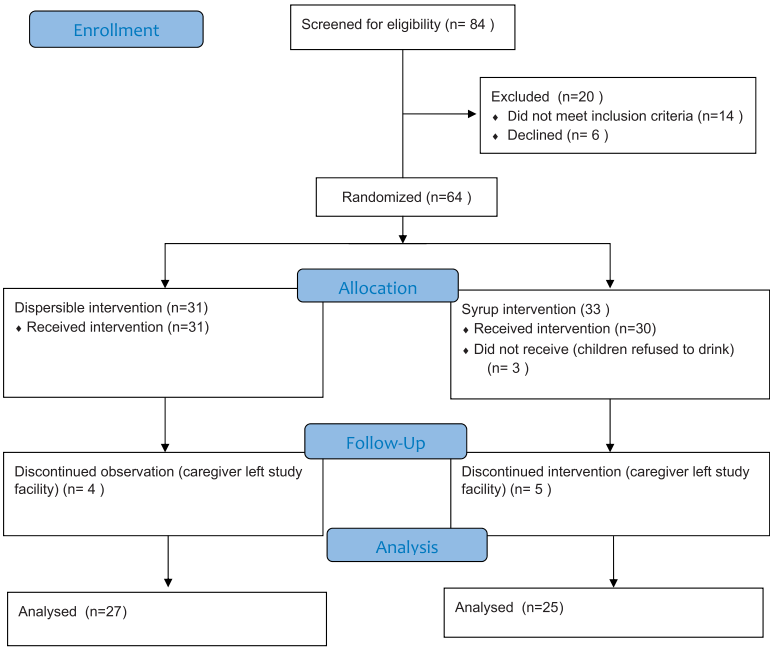

Figure 1. Flow chart of the study.

Table 1. Age demographics of participants.

		Paracetamol formulation		
		Dispersible	Syrup	Total
Age group	<1 year	5 (18.50%)	11 (44.00%)	16 (30.80%)
	1–4 years	16 (59.30%)	9 (36.00%)	25 (48.10%)
	>4 years	6 (22.20%)	5 (20.00%)	11 (21.20%)

Table 2. Comparison of mean temperatures within and between groups.

	Paracetamol formulation			
Time	Dispersible, n	Syrup, n	t	P value
T1	*38.20 ± 0.46	*38.32 ± 0.58	0.861	0.393
T2	*37.97 ± 1.10	*38.02 ± 1.07	0.139	0.890
T3	37.55 ± 0.20	37.66 ± 0.45	1.136	0.261
F	6.018	5.018		
P value	0.004	0.009		

T1, baseline temperature; T2, 30 minutes; T3, 60 minutes.
*Duncan Multiple comparison test indicating means not significantly different.

Table 3. Comparison of changes from baseline temperatures between dispersible and syrup drug groups.

	Paracetamol formulation			
Time	Dispersible Change from baseline mean (%)	Syrup Change from baseline mean (%)	T	P value
T2	0.23°C (0.6)	0.31°C (0.8)	0.320	0.750
T3	0.65°C (1.7)	0.67°C (1.7)	0.096	0.924

T2, 30 minutes; T3, 60 minutes.

At time T2, the dispersible group showed a decrease in temperature by 0.6% (mean, 0.23°C) compared with 0.8% (mean, 0.31°C) in the syrup group, and the result was not significantly different. Similarly, at time T3, there was no statistically significant difference in temperature in the dispersible group [decreased by 1.7% (mean, 0.65°C)] compared with the control group [decreased by 1.7% (mean, 0.67°C)] (Table 3). Although most patients still had fever after 60 minutes (Table 4), there was a decreasing trend in the proportion of patients with fever.

Discussion

The development of drug formulations for children is a complex process requiring an understanding of the interplay between factors, such as age, taste preferences and caregiver convenience. Paracetamol is a widely used analgesic and antipyretic in the paediatric population. Many forms are available in the market, the choice of which is determined by the dose required, state of the patient and ease of administration. The oral route is the most preferred across all age groups.[12]

Table 4. Comparison of the number of febrile participants in each arm of the study.

	Paracetamol formulation			
	Dispersible, n (%)	Syrup, n (%)	χ^2	P value
T1				
Fever (≥37.5°C)	27 (100.0)	25 (100.0)	NA	NA
No fever	0 (0.0)	0 (0.0)		
T2				
Fever (≥37.5°C)	18 (66.7)	18 (72.0)	0.173	0.677
No fever	9 (33.3)	7 (28.0)		
T3				
Fever (≥37.5°C)	25 (92.6)	23 (92.0)	0.006	0.936
No fever	2 (7.4)	2 (8.0)		

T1, baseline temperature; T2, 30 minutes; T3, 60 minutes.
NA = Not Applicable.

This study showed that the children still had fever 1 hour after the intervention in both study arms, although their mean temperatures exhibited a decreasing trend. This is not unexpected because of the duration of the study. The peak plasma concentration of paracetamol occurs between 30 minutes to 2 hours, and the peak effect is observed between 1 to 3 hours. Therefore, more time was likely needed to observe the antipyretic effect of each medication. The comparative study by Karbasi et al.[13] that investigated the antipyretic efficacy of oral and rectal paracetamol documented fever in both arms of the study up to three hours after the intervention, although there was a significant decrease in the degree of fever.

There was no statistically significant difference between the two groups at 30 minutes or 1 hour after the intervention. No studies have compared the efficacy of dispersible tablets and syrups of paracetamol in children. However, identical efficacies of equal doses of rectal and oral paracetamol have been documented previously by several studies.[13–16] Fathi et al.[17] compared the bioavailability of dispersible, capsule and tablet formulations of paracetamol and noted significant differences between them after 1 hour of ingestion, with dispersible paracetamol having the highest bioavailability. Because this study was conducted among adults, syrup was not included.

Dispersible tablets, sprinkles, powders and other modalities were developed to achieve increased drug stability compared with liquid forms.[18–20] These are manufactured in the solid state and remain in this form until use. This may have triggered the development of dispersible paracetamol.

The choice of formulation between syrup and dispersible paracetamol is dependent on the convenience of the caregiver and acceptability of the brand (flavour, colour) but not efficacy because this study demonstrated equal efficacy. Additionally, most antipyretics have other associated effects, such as analgesia, which can also affect a caregiver's decision to use the product even in the absence of fever. However, the use of paracetamol for the treatment of pain in children has been reported to be often underdosed.[21] Similarly, fever phobia is a well-documented global phenomenon, and this has been associated with the pattern of antipyretic use by both caregivers and health workers.[22–24]

The study participants were given newly opened syrup formulations, and further

studies may be required to demonstrate sustained efficacy over the time that the drug is being used. This is because of the possible effects of temperature, humidity and light on the opened syrup formulation. Syrups may lose flavour, change state or even precipitate. Similarly, tablets (dispersible inclusive) may disintegrate, harden or have altered dissolution times if exposed overtime before use.

The duration of the study was a limitation. This was mainly because the participants were outpatients who ended up not staying for the initially proposed duration of 4 hours, as they needed to leave and start their prescribed medications. This development limited the observation of the temperature changes in the study participants.

Conclusion

The antipyretic efficacy of dispersible paracetamol and paracetamol syrup in paediatric patients was compared. The decreasing trend in temperature was similar in both groups. Both preparations produced statistically similar antipyretic effects with no reported adverse drug reaction.

Acknowledgements

The authors acknowledge the support of the staff and patients of the Child Health Department of Polyclinic District Hospital Asata, Enugu, Nigeria.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Funding

This study received funding from the African Research League, College of Medicine, University of Nigeria Ituku-ozalla.

Author contributions

OB: Conceptualized the study, contributed to data collection, data analysis and writing of the initial draft and approved the final version of the manuscript.
IB: Contributed to conceptualizing the study, data collection and data analysis and approved the final version of the manuscript
AB: Contributed to data collection and data analysis, wrote the final draft and approved the final version of the manuscript.

ORCID iDs

Benjamin Okereke https://orcid.org/0000-0002-6942-3939
Okezie Ibeleme https://orcid.org/0000-0001-9341-1017
Adaobi Bisi-Onyemaechi https://orcid.org/0000-0001-8416-6312

References

1. Whitburn S, Costelloe C, Montgomery AA, et al. The frequency distribution of presenting symptoms in children aged six months to six years to primary care. *Prim Health Care Res Dev* 2011; 12: 123–134. doi: 10.1017/S146342361000040X.
2. De Bont EGPM, Lepot JMM, Hendrix DAS, et al. Workload and management of childhood fever at general practice out-of-hours care: An observational cohort study. *BMJ Open* 2015; 5: e007365. doi: 10.1136/bmjopen-2014-0073654.
3. Sands R, Shanmugavadivel D, Stephenson T, et al. Medical problems presenting to paediatric emergency departments: 10 years on. *Emerg Med J* 2012; 29: 379–382. doi: 10.1136/emj.2010.106229.
4. NHS Inform. Fever in Children. (accessed 28 December 2020) https: //www.nhsinform.scot/illnesses-and-conditions/infections-and-poisoning/fever-in-children
5. WHO. Integrated Management of Childhood illnesses (IMCI). Fever, accessed 29 December 2020 at https: //apps.who.int/iris/bitstream/handle/10665/104772/9789241506823_Module-5_eng.pdf; jsessionid=64C72B23CDFB6296EF76337BA21979D8?sequence=7.
6. Atkins E. Fever; the old and the new. *J Infect Dis* 1984; 149: 339–348.
7. Plaisance KI and Mackowiak PA. Antipyretic therapy: physiologic rationale,

diagnostic implications, and clinical consequences. *Arch Intern Med* 2000; 160: 449–456.
8. Mackowiak PA. Physiological rationale for suppression of fever. *Clin Infect Dis* 2000; 31: S185–S189.
9. Ryan M and Levy MM. Clinical review: fever in intensive care unit patients. *Crit Care* 2003; 7: 221–225.
10. Mackowiak PA, Ruderman AE, Martin RM, et al. Effects of physiologic variations in temperature on the rate of antibiotic-induced bacterial killing. *Am J Clin Pathol* 1981; 76: 57–62.
11. Baker MD, Fosarelli PD and Carpenter RO. Childhood fever: Correlation of diagnosis with temperature response to acetaminophen. *Pediatrics* 1987; 80: 315–318.
12. Obu HA, Chinawa JM, Ubesie AC, et al. Paracetamol use (and/or misuse) in children in Enugu, South-East, Nigeria. *BMC Pediatr* 2012; 12: 103.
13. Karbasi SA, Modares-Mosadegh M and Golestan M. Comparison of antipyretic effectiveness of equal doses of rectal and oral acetaminophen in children. *J Pediatr (Rio J)* 2010; 86: 228–232. doi.org/10.1590/S0021-75572010000300011
14. Nabulsi M, Tamim H, Sabra R, et al. Equal antipyretic effectiveness of oral and rectal acetaminophen: a randomized controlled trial [ISRCTN11886401]. *BMC Pediatr* 2005; 5: 35.
15. Vernon S, Bacon C and Weightman D. Rectal paracetamol in small children with fever. *Arch Dis Child* 1979; 54: 469–470.
16. Scolnik D, Kozer E, Jacobson S, et al. Comparison of oral versus normal and high-dose rectal acetaminophen in the treatment of febrile children. *Pediatrics* 2002; 110: 553–556.
17. Fathi M, Kazemi S, Tajrishi FZ, et al. Comparison of oral bioavailability of acetaminophen tablets, capsules and effervescent dosage forms in healthy volunteers. *Current Issues in Pharmacy and Medical Sciences* 31: 5–9. DOI: 10.1515/cipms-2018-0001
18. Batchelor HK and Marriott JF. Formulations for children: problems and solutions. *Br J Clin Pharmacol* 2015; 79: 405–418.
19. Van Riet-Nales DA, Schobben AFAM, Vromans H, et al. Safe and effective pharmacotherapy in infants and preschool children: importance of formulation aspects. *Arch Dis Child* 2016; 101: 662–669. doi: 10.1136/archdischild-2015-308227
20. Strickley RG. Pediatric Oral Formulations: An Updated Review of Commercially available Pediatric Oral Formulations Since 2007. *J Pharm Sci* 2019; 108: 1335–1365.
21. Milani GP, Benini F, Dell'Era L, et al. Acute pain management: acetaminophen and ibuprofen are often under-dosed. *Eur J Pediatr* 2017; 176: 979–982. doi: 10.1007/s00431-017-2944-6.
22. Clericetti CM, Milani GP, Bianchetti MG, et al. Systematic review finds that fever phobia is a worldwide issue among caregivers and healthcare providers. *Acta Paediatr* 2019; 108: 1393–1397. doi: 10.1111/apa.14739.
23. Sakai R, Okumura A, Marui E, et al. Does fever phobia cross borders? The case of Japan. *Pediatr Int* 2012; 54: 39–44. doi: 10.1111/j.1442-200X.2011.03449.x.
24. Purssell E and Collin J. Fever phobia: The impact of time and mortality–a systematic review and meta-analysis. *Int J Nurs Stud* 2016; 56: 81–89. doi: 10.1016/j.ijnurstu.2015.11.001.