

Rectal Diclofenac Versus Rectal Paracetamol: Comparison of Antipyretic Effectiveness in Children

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Abstract

Background: Fever is the most common complaint in pediatric medicine and its treatment is recommended in some situations. Paracetamol is the most common antipyretic drug, which has serious side effects such as toxicity along with its positive effects. Diclofenac is one of the strongest non-steroidal anti-inflammatory (NSAID) drugs, which has received little attention as an antipyretic drug.

Objectives: This study was designed to compare the antipyretic effectiveness of the rectal form of Paracetamol and Diclofenac.

Patients and Methods: This double-blind controlled clinical trial was conducted on 80 children aged six months to six years old. One group was treated with rectal Paracetamol suppositories at 15 mg/kg dose and the other group received Diclofenac at 1 mg/kg by rectal administration (n = 40). Rectal temperature was measured before and one hour after the intervention. Temperature changes in the two groups were compared.

Results: The average rectal temperature in the Paracetamol group was $39.6 \pm 1.13^\circ\text{C}$, and $39.82 \pm 1.07^\circ\text{C}$ in the Diclofenac group ($P = 0.37$). The average rectal temperature, one hour after the intervention, in the Paracetamol and the Diclofenac group was $38.39 \pm 0.89^\circ\text{C}$ and $38.95 \pm 1.09^\circ\text{C}$, respectively ($P = 0.02$). Average temperature changes were $0.65 \pm 0.17^\circ\text{C}$ in the Paracetamol group and $1.73 \pm 0.69^\circ\text{C}$ in the Diclofenac group ($P < 0.001$).

Conclusions: In the first one hour, Diclofenac suppository is able to control the fever more efficient than Paracetamol suppositories.

Keywords: Diclofenac, Fever, Paracetamol, Rectal Administration

1. Background

Fever, defined as a rectal temperature higher than 38°C , is the most common complaint among children admitted to emergency departments (1). Infectious and noninfectious triggers cause a release of pyrogenic cytokine such as interleukin-1, interleukin-6, Tumor Necrosis Factor-alpha (TNF- α) and Interferon-gamma (IFN- γ). These cytokines in turn act on the thermoregulatory center of the hypothalamus, which leads to an increase in temperature set point, thus causing fever (2, 3). Fever, as a part of an effective immune system, improves the immunological response and slows growth and replication of viral and bacterial pathogens (4). Increased metabolic reactions, increased oxygen consumption, and increased heart and lung function are some effects of fever, which may lead to dangerous outcomes, especially in children with underlying diseases (5). Although fever is mostly self-limited in children and usually the underlying cause of fever should be treated, yet antipyretic therapy is also

indicated when there is fever higher than 39°C , an underlying disease (such as any cardiac, pulmonary or neurologic problems), discomfort or hemodynamic and electrolyte imbalance (3, 6, 7).

Paracetamol (acetaminophen) is an antipyretic and analgesic medication, most frequently used in pediatrics for both outpatient and admitted patients. The mechanism of action of this drug is not fully understood, yet it is postulated that the acetaminophen-induced antipyresis occurs via central inhibition of the enzyme Cyclooxygenase (COX). Acetaminophen does not inhibit COX in peripheral tissues and, thus, has no peripheral anti-inflammatory effects and is not classified as a member of the non-steroidal anti-inflammatory drugs (NSAIDs) (2, 8). Despite its favorable effects, poisoning, kidney failure and hepatotoxicity are the most serious adverse effects of Paracetamol, which may occur due to acute exposure (9).

Diclofenac is a non-steroidal anti-inflammatory drug

(NSAID), which has analgesic and antipyretic activities. This drug is readily absorbed from the alimentary tract, and its half time is about one to two hours, and it will quickly dissolve in an environment with a pH higher than five. Diclofenac as one of the most potent NSAID has a few side effects when administered rectally (10). Antipyretic effects of this drug have received less attention in comparison with its analgesic effects (11, 12).

2. Objectives

Considering the importance of fever and unknown antipyretic properties of Diclofenac in the pediatric population, this clinical trial was designed and implemented in order to compare the antipyretic effectiveness of Paracetamol and Diclofenac, administered rectally.

3. Patients and Methods

3.1. Study Participants

This double-blind controlled clinical trial comprised of 80 children aged one to six years, and was conducted from October 2012 to November 2013, at Shahid Beheshti hospital of Kashan, Iran. Shahid Beheshti hospital has 393 active beds in 16 different specialist units including pediatric, internal medicine, obstetrics and gynecology, infectious diseases, dermatology, cardiology and intensive care. This specialty and subspecialty hospital is a public hospital and is considered a regional referral center.

Children whose rectal temperatures were higher than 38°C and those who had fevers of less than four days were entered in the study. Convenience sampling was used and all patients meeting the least required criteria, who had visited our health center since the beginning of the study until completion of the required sample size, were selected. Those who had received other antipyretic agents, had undergone non pharmacological interventions to control the fever, had diarrhea, had a history of allergic reactions to Paracetamol and/or Diclofenac, had any anomalies of the gastrointestinal tract, had been affected by chronic diseases and those whose parents refused to participate, were excluded from the study. The total number of recruited cases was 87. However, due to diarrhea (four cases), having had received oral Paracetamol prior to the visit (two cases) and having had a history of imperforate anus (one case) seven cases were excluded, thus the final sample size was 80. After being informed of the study objectives, the participants' parents signed a written consent form to participate in the study. Then a questionnaire, which asked for the child's age, gender, weight and possible diagnosis, was completed.

Patients were randomly allocated to two groups of Paracetamol and Diclofenac using a permuted-block randomization scheme. For this purpose, 20 blocks with a block size of four were used and the blocks were classi-

fied in order of numbers. Two researchers were involved in this study. One of them was responsible for sampling, completing the questionnaires, allocating the patients to different treatment groups and preparation and administration of the drugs. The other one was responsibility for simply measuring the rectal temperature of the child under study before and after the intervention. This researcher was totally unaware of patient allocation, to avoid bias. The parents did not know the type of treatment, either (Figure 1).

All ethical principles were respected in accordance with resolution 196/96 on research involving human subjects. The ethics committee of Kashan University of Medical Sciences (Approval code: 29/5/1/2742/P) approved the study and supervised all stages. This study was also recorded in the Iran center of clinical trials registration database (IRCT2012101711145N1).

However, since the antipyretic effects of rectal forms of Paracetamol and Diclofenac have not been compared so far, to determine the required sample size we used the same methodology as was performed in a previous evaluation to compare the analgesic effects of rectal forms of these two drugs. In their study, the mean pain score one hour after the surgery was 7.8 ± 2.25 in the Paracetamol group and 6.4 ± 0.8 in the Diclofenac group (11). With a power of 90% and $Z_{1-\alpha/2} = 1.28$, and using the equation following equation, the minimum sample size required in each group was calculated to be 31 cases (Equation 1).

$$(1) \quad \frac{\left(z_{1-\frac{\alpha}{2}} + z_{1-\beta}\right)^2 (\sigma_1^2 + \sigma_2^2)}{(\mu_1 - \mu_2)^2}$$

Taking into account our medical facilities and to allow for losses, we finally estimated a sample size of 40 cases in each group.

3.2. Body Temperature Measurement

Body temperature of the studied children was measured shortly before the intervention. The MT 19Fi digital thermometer, manufactured by Microlife® Company, was used for measuring temperature.

This thermometer registers the rectal temperature in degrees Celsius within 10 seconds and displays it digitally. The equipment was calibrated by the manufacturing company, and to evaluate the reliability of the measurements, all recordings were compared with the results obtained with a glass mercury thermometer before the study.

The thermometer was disinfected with 70% alcohol and the tip was lubricated with Vaseline. Supervised by the researcher, the tip of thermometer was gently inserted about 2 cm into the child's rectum by the parents, and then the registration key was pressed. Rectal temperatures were recorded after 10 seconds. Temperature was measured again one hour after the intervention by the same method.

Rectal temperatures greater than or equal to 38°C were labeled as a fever. The rate of temperature change after treatment in each group was calculated and recorded. Fever reduction rate of more than 0.1°C was considered as success. Three classes of successful treatment were low recovery rate from 0.5 to 0.1, average recovery rate from 1 to 0.6, and high recovery rate of more than 1°C temperature decrease.

3.3. Medications

Paracetamol and Diclofenac suppositories were administered per rectum at 15 mg/kg and 1 mg/kg dose, respectively. One hundred and twenty-five milligrams and 325 mg Paracetamol suppositories, and 100 mg and 50 mg Diclofenac suppository of Aboureihan Company (Iran) were used for this purpose. To determine the amount of medication required per dose, the suppositories were scraped-off using a very sharp surgical blade, sectioned longitudinally, and weighed by AND® digital scale (made in Japan) with accuracy of 0.001 g. The drug was then converted into the usable form. All stages of drug preparation were done by an expert pharmacist.

After instructing the parents, the drug was inserted into the child's rectum slowly by the parents under supervision of the researcher.

3.4. Statistical Analysis

Data was analyzed using the SPSS version 18 software for Windows. The descriptive part of the analysis was reported as absolute and relative frequencies. Baseline variables, fever reduction grade and fever after treatment were analyzed by the Chi-square and Fisher's exact tests. The results of the quantitative data analysis were expressed as mean \pm standard deviation. Kolmogorov-Smirnov was applied to assess the data distribution. According to the normal distribution of age, weight and primary and secondary temperature data, independent t test and paired t test were used to compare the averages. Mann-Whitney U test was used for comparison of average temperature decrease due to abnormal data distribution. Repeated measure Analysis of Variance (ANOVA) was also used to compare the average body temperature at different study times. All tests were two-tailed. The level of significance for all tests was considered as $P < 0.05$.

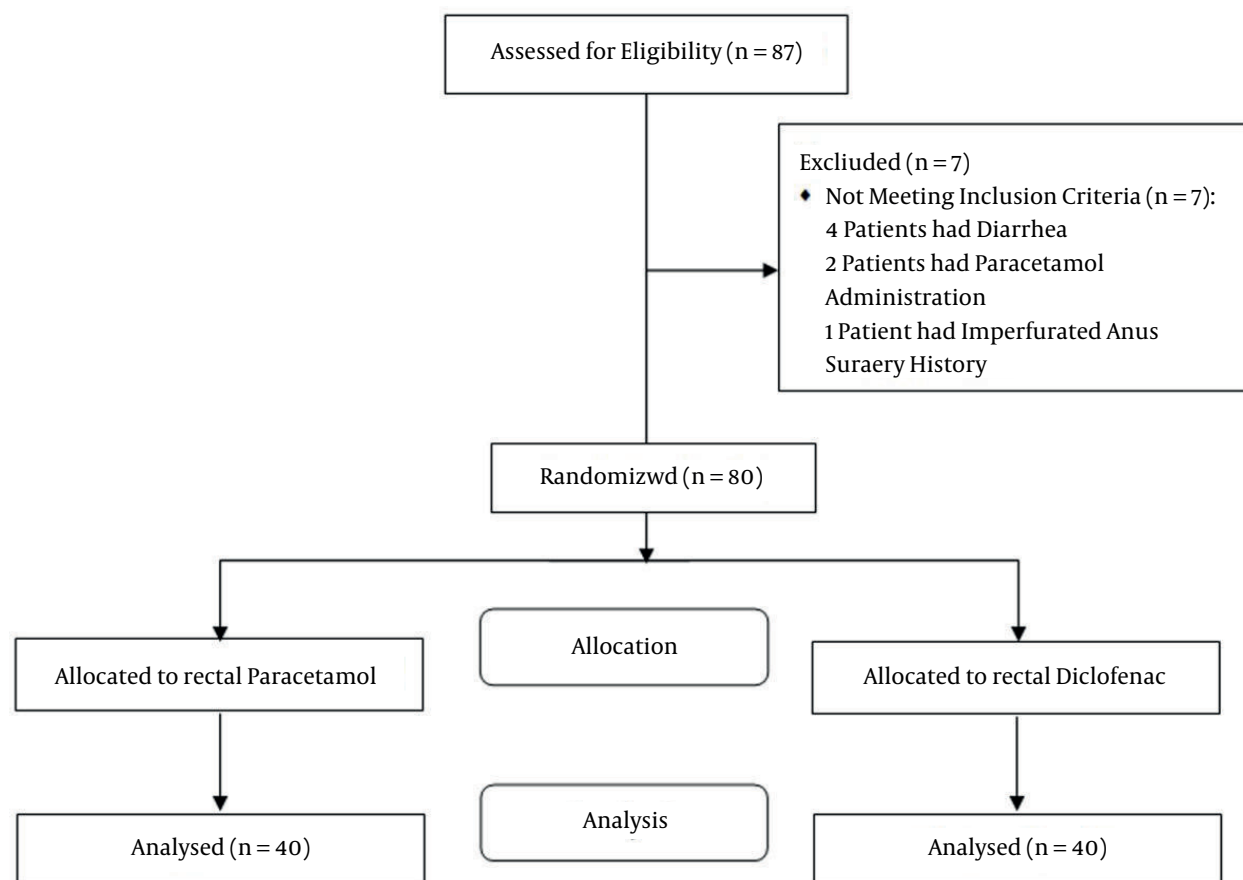


Figure 1. Study Flow Chart

Table 1. Baseline Characteristics

Characteristics	Groups (n = 40)		P Value
	Diclofenac	Paracetamol	
Age			0.27
Mean ± SD	3.17 ± 1.41	3.55 ± 1.58	
Range	1 - 6	1 - 6	
Weight			0.28
Mean ± SD	14.56 ± 2.74	15.29 ± 3.21	
Range	9.3 - 20.6	8.1 - 20.5	
Gender^a			0.37
Male	19 (47.5)	23 (57.5)	
Female	21 (52.5)	17 (42.5)	
Temperature			0.37
Mean ± SD	39.82 ± 1.07	39.6 ± 1.13	
Range	38 - 41.5	38 - 41.5	
Diagnosis^a			0.89
URTI	15 (37.5)	16 (40.0)	
LRTI	8 (20.0)	10 (25.0)	
UTI	7 (17.5)	5 (12.5)	
Otitis	4 (10.0)	5 (12.5)	
Other	6 (15.0)	4 (10.0)	

Abbreviations: LRTI, lower respiratory tract infection; UTI, urinary tract infection; URTI, upper respiratory tract infection.

^aValues are expressed as No.(%).

4. Results

A total of eighty children were examined in two treatment groups of Paracetamol and Diclofenac. All patients completed the study and no drug-related allergic reactions were observed. Baseline characteristics of patients are shown in Table 1.

Reduced temperature of at least 0.1°C was detected in all patients in both groups. The average temperature one hour after the procedure was 38.39 ± 0.89°C in the Diclofenac group, which was significantly reduced compared to the initial temperature ($P < 0.001$). The mean temperature was 38.95 ± 1.09°C for the Paracetamol group, which had also significantly decreased compared to the initial temperature ($P < 0.001$).

The average temperatures of patients before and after the intervention were compared using the repeated measures ANOVA. Despite the significant decrease in the measured temperatures, there were no significant differences between the two groups ($P = 0.47$) (Figure 2).

The amount of temperature reduction was significantly greater in the Diclofenac group. Treatment results in the studied groups are shown in Table 2.

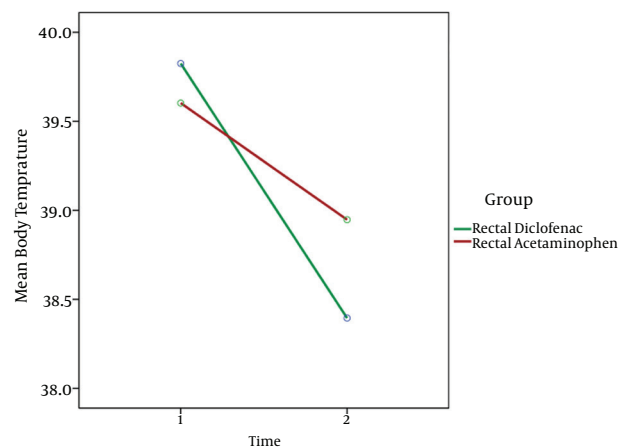


Figure 2. Temperature Changes of Patients in the Studied Groups

Table 2. Treatment Outcomes

Outcome	Groups (n = 40)		P Value
	Diclofenac	Paracetamol	
Temperature Reduction			< 0.001
Mean ± SD	1.43 ± 0.69	0.65 ± 0.17	
Range	0.8 - 3.8	0.4 - 0.9	
Median (IQR)	1.3 - 0.6	0.6 - 0.3	
Reduction Grad^a			< 0.001
Low	0	16 (41.0)	
Moderate	14 (35.0)	23 (59.0)	
High	26 (65.0)	0	
Fever after treatment^a			0.1
No	17 (42.5)	10 (25.0)	
Yes	23 (57.5)	30 (75.0)	

^aValues are expressed as No. (%).

5. Discussion

This study was conducted to compare the antipyretic effectiveness of the suppository form of Paracetamol versus Diclofenac. Both Diclofenac and Paracetamol proved to be successful in reducing temperature, yet Diclofenac had a greater antipyretic effect than Paracetamol.

Oral and rectal forms of Paracetamol are among the most popular and widely used over-the-counter drugs for the treatment of pain and fever, especially in the pediatric population (13, 14). In previous studies, the antipyretic effect of rectal paracetamol has been well established, yet the antipyretic effect after one hour of administration has not been clarified (15-17). To best of our knowledge, only one study has reported a decrease in body temperature one hour following the administration of Paracetamol with an average of $1.07 \pm 0.16^{\circ}\text{C}$, which is significantly more than what we detected in our survey ($0.65 \pm 0.17^{\circ}\text{C}$) (17). These differences are hard to explain as the same drugs, dose and methods had been used. However the initial body temperature (39°C in the study of Karbasi et al. (17) and 38°C in our study) could be the cause of these differences.

Unlike Paracetamol, antipyretic properties of NSAIDs, especially Diclofenac, are somewhat unknown and only a few studies have examined these effects (18-22). In one study, that examined the effect of different doses of oral Diclofenac in reducing fever and pain, resulting from acute febrile sore throat, Diclofenac significantly reduced fever and throat pain. The overall efficacy of all doses of Diclofenac (6.25, 12.5 and 25 mg) was rated significantly higher than that of the placebo. Also, Paracetamol was only slightly better than Diclofenac 6.25 mg dose, and the other doses of Diclofenac proved to be more effective as compared to Paracetamol (22).

The study of Polman et al. on the antipyretic effect of suppository Diclofenac showed that it significantly decreases

fever during the first two hours after administration and the body temperature returns to normal values after two hours in all patients receiving Diclofenac (18). Litalien et al. studied the efficacy of NSAIDs including suppository Diclofenac in reduction of fever and pain in children and reported it to be more effective than oral acetaminophen. Also, suppository Diclofenac was more effective in relieving pain compared to acetaminophen (19).

We believe that this is the first attempt that compares the antipyretic effectiveness of the rectal forms of Paracetamol and Diclofenac. Diclofenac is rapidly absorbed in those parts of the gastrointestinal tract that have pH values higher than five (23). Paracetamol is also highly absorbed under alkaline conditions; however, its absorption is less dependent on the environmental pH (24, 25). The alkaline environment of the rectum has a relatively similar impact on the absorption of both drugs (26). So what makes Diclofenac more efficient in reducing fever is the variability of the time when maximum concentrations of the drugs are reached, which is one hour for Diclofenac and more than two hours for Paracetamol (27-29). The antipyretic effect during the following hours was not evaluated in this study yet considering the half-life of Diclofenac (which is about 80 to 120 minutes) and Paracetamol (which is about six to eight hours), it is postulated that over the following hours the degree of reduction in fever becomes similar in both groups (27).

The ability of Diclofenac to quickly reduce the body temperature makes this drug a suitable choice for children's fever treatment especially in those patients with poor or critical conditions; however, its short half-life may increase the likelihood of recurrent fever. Conducting trials, which simultaneously assess antipyretic and analgesic effect of Paracetamol and Diclofenac may help identify the advantages of each.

As previously stated, to best of our knowledge, this study is the first completed clinical trial comparing the antipyretic properties of rectal forms of Diclofenac and Paracetamol. One of the strengths of the present study is that the drug administration was based on the patients' total body weight achieved through accurate measurement and converting the drugs. This method greatly eliminated errors associated with inadequate dosing.

This study had some limitations, one of which was the impossibility of assessing the adverse effects of the studied drugs as they were used with other drugs and at a single dose. Not measuring the serum levels of the drugs in studied subjects is considered the other limitation, which prevented the evaluation of the inter-individual differences in absorbing the drugs and the time of maximum serum concentrations. The last limitation involves non-cooperative parents, who refused to check the rectal temperature frequently during the following hours.

In conclusion, this study showed that suppository Diclofenac could significantly decrease rectal temperature as compared with suppository Paracetamol during the first hour, yet overall both drugs were found to be equally effective for stopping fever. Finally, a similar study with a larger population is warranted to investigate the extent of temperature control at different elapsed times after medication administration in order to better compare the efficacy of these two drugs.

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Footnotes

Author's Contribution:Development of the original idea: Mohammad Reza Sharif; study concept and design: Mohammad Reza Sharif and Masoud Rangraz; data collection: Masoud Rangraz, Golbahareh Sarami and Marzieh Aalinezhad; analysis and interpretation of data: Mostafa Haji Rezaei and Marzieh Aalinezhad; preparation of the manuscript: Masoud Rangraz and Mostafa Haji Rezaei; revision of the manuscript: Mohammad Reza Sharif and Masoud Rangraz.

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References

- Claudius I, Baraff LJ. Pediatric emergencies associated with fever. *Emerg Med Clin North Am.* 2010;**28**(1):67-84. doi: 10.1016/j.emc.2009.09.002. [PubMed: 19945599]
- van den Anker JN. Optimising the management of fever and pain in children. *Int J Clin Pract Suppl.* 2013;**178**:26-32. doi: 10.1111/ijcp.12056. [PubMed: 23163545]
- Dayal R, Agarwal, D. Fever in Children and Fever of Unknown Origin. *Indian J Pediatr.* 2015;1-6. doi: 10.1007/s12098-015-1724-4.
- Dixon G, Booth C, Price E, Westran R, Turner M, Klein N. Fever as nature's engine. Part of beneficial host response? *BMJ.*

- 2010;**340**:c450. doi:10.1136/bmj.c450. [PubMed: 20103514]
- Wright AD, Liebelt EL. Alternating antipyretics for fever reduction in children: an unfounded practice passed down to parents from pediatricians. *Clin Pediatr (Phila).* 2007;**46**(2):146-50. doi: 10.1177/0009922806293922. [PubMed: 17325087]
- Avner JR. Acute fever. *Pediatr Rev.* 2009;**30**(1):5-13. doi: 10.1542/pir.30-1-5. [PubMed: 19118137]
- El-Radhi AS. Why is the evidence not affecting the practice of fever management? *Arch Dis Child.* 2008;**93**(11):918-20. doi: 10.1136/adc.2008.139949. [PubMed: 18562453]
- Graham GG, Davies MJ, Day RO, Mohamudally A, Scott KF. The modern pharmacology of paracetamol: therapeutic actions, mechanism of action, metabolism, toxicity and recent pharmacological findings. *Inflammopharmacology.* 2013;**21**(3):201-32. doi: 10.1007/s10787-013-0172-x. [PubMed: 23719833]
- Star K, Choonara I. How safe is paracetamol? *Arch Dis Child.* 2015;**100**(1):73-4. doi: 10.1136/archdischild-2014-307431. [PubMed: 25512959]
- Derry S, Rabbie R, Moore RA. Diclofenac with or without an antiemetic for acute migraine headaches in adults. *Cochrane Database Syst Rev.* 2013;**4**:CD008783. doi: 10.1002/14651858.CD008783.pub3. [PubMed: 23633360]
- Mireskandari SM, Makarem J. Effect of rectal diclofenac and acetaminophen alone and in combination on postoperative pain after cleft palate repair in children. *J Craniofac Surg.* 2011;**22**(5):1955-9. [PubMed: 21959480]
- Standing JF, Tibboel D, Korpela R, Olkkola KT. Diclofenac pharmacokinetic meta-analysis and dose recommendations for surgical pain in children aged 1-12 years. *Paediatr Anaesth.* 2011;**21**(3):316-24. doi: 10.1111/j.1460-9592.2010.03509.x. [PubMed: 21276131]
- Jensen JF, Tonnesen LL, Soderstrom M, Thorsen H, Siersma V. Paracetamol for feverish children: parental motives and experiences. *Scand J Prim Health Care.* 2010;**28**(2):115-20. doi: 10.3109/02813432.2010.487346. [PubMed: 20470019]
- Temple AR, Temple BR, Kuffner EK. Dosing and antipyretic efficacy of oral acetaminophen in children. *Clin Ther.* 2013;**35**(9):1361-75. doi: 10.1016/j.clinthera.2013.06.022. [PubMed: 23972576]
- Nabulsi M, Tamim H, Sabra R, Mahfoud Z, Malaeb S, Fakh H, et al. Equal antipyretic effectiveness of oral and rectal acetaminophen: a randomized controlled trial [ISRCTN1886401]. *BMC Pediatr.* 2005;**5**:35. doi: 10.1186/1471-2431-5-35. [PubMed: 16143048]
- Scolnik D, Kozer E, Jacobson S, Diamond S, Young NL. Comparison of oral versus normal and high-dose rectal acetaminophen in the treatment of febrile children. *Pediatrics.* 2002;**110**(3):553-6. [PubMed: 12205259]
- Karbasi SA, Modares-Mosadegh M, Golestan M. Comparison of antipyretic effectiveness of equal doses of rectal and oral acetaminophen in children. *J Pediatr (Rio J).* 2010;**86**(3):228-32. doi: 10.2223/JPED.1992. [PubMed: 20436978]
- Polman HA, Huijbers WA, Augusteijn R. The use of diclofenac sodium (Voltaren) suppositories as an antipyretic in children with fever due to acute infections: a double-blind, between-patient, placebo-controlled study. *J Int Med Res.* 1981;**9**(5):343-8. [PubMed: 7028533]
- Litalien C, Jacqz-Aigrain E. Risks and benefits of nonsteroidal anti-inflammatory drugs in children: a comparison with paracetamol. *Paediatr Drugs.* 2001;**3**(11):817-58. [PubMed: 11735667]
- Anderson BJ. Comparing the efficacy of NSAIDs and paracetamol in children. *Paediatr Anaesth.* 2004;**14**(3):201-17. [PubMed: 14996259]
- Bradley RL, Ellis PE, Thomas P, Bellis H, Ireland AJ, Sandy JR. A randomized clinical trial comparing the efficacy of ibuprofen and paracetamol in the control of orthodontic pain. *Am J Orthod Dentofacial Orthop.* 2007;**132**(4):511-7. doi: 10.1016/j.ajodo.2006.12.009. [PubMed: 17920505]
- Gehanno P, Dreiser RL, Ionescu E, Gold M, Liu JM. Lowest effective single dose of diclofenac for antipyretic and analgesic effects in acute febrile sore throat. *Clin Drug Investig.* 2003;**23**(4):263-71. [PubMed: 17535039]
- Jilani JA, Idkaidek NM, Alzoubi KH. Synthesis, In Vitro and In Vivo Evaluation of the N-ethoxycarbonylmorpholine Ester of Diclofenac.

- enac as a Prodrug. *Pharmaceuticals (Basel)*. 2014;**7**(4):453-63. doi: 10.3390/ph7040453. [PubMed: 24736104]
24. Krasniak AE, Knipp GT, Svensson CK, Liu W. Pharmacogenomics of acetaminophen in pediatric populations: a moving target. *Front Genet*. 2014;**5**:314. doi: 10.3389/fgene.2014.00314. [PubMed: 25352860]
 25. Singla NK, Parulan C, Samson R, Hutchinson J, Bushnell R, Beja EG, et al. Plasma and cerebrospinal fluid pharmacokinetic parameters after single-dose administration of intravenous, oral, or rectal acetaminophen. *Pain Pract*. 2012;**12**(7):523-32. doi: 10.1111/j.1533-2500.2012.00556.x. [PubMed: 22524979]
 26. Turner C, Aye Mya Thein N, Turner P, Nosten F, White NJ. Rectal pH in well and unwell infants. *J Trop Pediatr*. 2012;**58**(4):311-3. doi: 10.1093/tropej/fmr088. [PubMed: 21984527]
 27. van der Marel CD, Anderson BJ, Romsing J, Jacqz-Aigrain E, Tibboel D. Diclofenac and metabolite pharmacokinetics in children. *Paediatr Anaesth*. 2004;**14**(6):443-51. doi: 10.1111/j.1460-9592.2004.01232.x. [PubMed: 15153204]
 28. Standing JF, Howard RF, Johnson A, Savage I, Wong IC. Population pharmacokinetics of oral diclofenac for acute pain in children. *Br J Clin Pharmacol*. 2008;**66**(6):846-53. doi: 10.1111/j.1365-2125.2008.03289.x. [PubMed: 19032726]
 29. Villeneuve E, Gosselin S, Whyte I. Four-hour acetaminophen concentration estimation after ingested dose based on pharmacokinetic models. *Clin Toxicol (Phila)*. 2014;**52**(5):556-60. doi: 10.3109/15563650.2014.902956. [PubMed: 24697801]