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Original Article

Randomized Open-Label Study to Compare the Safety and Efficacy of Paracetamol, Ibuprofen, and Mefenamic Acid in Febrile Children

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Abstract

Background: Fever is the most common symptom presenting in the OPDs. Antipyresis is one of the most usual therapeutic interventions done. The present study compares the efficacy and tolerability of three antipyretics: Paracetamol, ibuprofen, and mefenamic acid.

Methodology: We performed a prospective study involving children with fever admitted in the general ward. Children were blocked randomized into three groups based on antipyretic treatment. Each of the children received either oral paracetamol/ibuprofen/mefenamic acid. The temperature was recorded at admission, hourly for the first 3 h and thereafter 6th hourly for 24 h.

Results: The fall in mean temperature from the baseline at different observation points for the study groups are evaluated and shown in Table 1. At the end of 2 h, the fall in mean temperature from the baseline for the mefenamic acid group is maximum (1.85°F) as compared to the other two groups and is statistically significant (P = 0.028). Even at the end of 6 h, the fall in mean temperature for the mefenamic acid group is more (2.60°F) and is statistically significant (0.028).

Conclusion: Mefenamic acid has better efficacy and tolerability when compared to paracteamol and ibuprofen.

Key words: Ibuprofen, Mefenamic acid, Paracetamol

INTRODUCTION

Fever is the most important and presenting symptom in pediatric clinics, OPDs, and Emergency. The normal body temperature is 36.5–37.5°C (97.7–99.5°F). Fever is defined as having a temperature above the normal range due to an increase in the body's temperature set-point.[1,2]

Hypothalamus is the body's thermoregulatory center that regulates the set-point at which the temperature of the body is maintained. Fever, however, is not the primary illness but is a physiological mechanism that has beneficial effects in fighting infection. A rise in body temperature by 1°C increases the neutrophil and macrophage activity almost double the normal. An increase in the temperature of the body puts the child under discomfort.

Administration of antipyretic is therefore one of the most common therapeutic measures. Non-steroidal anti-inflammatory drugs (NSAIDs) are the most frequently used antipyretics. Antipyretics are regularly prescribed for febrile kids by most pediatricians.

Antipyretics are of various classes, including acetylsalicylic acid acetaminophen (paracetamol) and other anti-inflammatory non-steroidal agents (NSAIDs) represented by indomethacin, mefenamic acid, and ibuprofen. "NSAIDs inhibit cyclooxygenase (COX) that catalyzes arachidonic acid transformation to prostaglandin E2. This decrease in prostaglandin E2 in the brain is thought to reduce the hypothalamic set-point to normal."[1,2]

At present, paracetamol, mefenamic acid, and ibuprofen are the preferred antipyretics used to treat fever in kids. Acetaminophen (paracetamol) has been in use for a long time. Paracetamol's antipyretic effect is thought

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Table 1: Difference in fall of mean temperature between study groups

Difference in temp (h)	Paracetamol		Ibuprofen		Mefenamic acid		ANOVA *P*-value
	Mean	SD	Mean	SD	Mean	SD	
After 1	0.96	0.50	0.99	0.21	1.05	0.36	0.431
After 2	1.62	0.65	1.67	0.30	1.85	0.36	0.028*
After 3	2.04	0.78	2.14	0.35	2.26	0.54	0.152
After 6	2.28	0.79	2.44	0.51	2.60	0.57	0.028*
After 12	2.67	0.72	2.58	0.57	2.62	0.71	0.786
After 18	2.65	0.77	2.49	0.50	2.68	0.75	0.301
After 24	2.52	0.63	2.48	0.54	2.60	0.65	0.585

*Significant at 5% level of significance ($P<0.05$)

to be caused by its ability to diminish the synthesis of prostaglandin in the brain. Since paracetamol in the periphery does not inhibit prostaglandin synthesis, it has no anti-inflammatory action. Paracetamol has potential side effects in addition to its beneficial effects and may even cause severe hypersensitivity reactions.

Ibuprofen is a propionic acid derivative which inhibits prostaglandin biosynthesis. Gastrointestinal bleeding is its side effect.

Mefenamic acid is a powerful cyclooxygenase inhibitor. It has both central and peripheral actions of an analgesic. This medication is commonly used in patients with osteoarthritis, rheumatoid arthritis, and dysmenorrhea.

Finding a cause for fever and treating it is crucial and providing efficient contemporary therapy is also important. It is necessary to consider the judicious use of antipyretics and to give due consideration to the side effects of antipyretics. The choice of an antipyretic should be determined by efficacy, safety, tolerability, duration of action, and cost of the particular antipyretic.

Paracetamol has been the most preferred antipyretic with the advantage of being a cheaper drug and is relatively safer. However, there have been reports of hepatotoxicity and liver failure with its overdosage. Recently, there has been an increasing trend regarding the use of mefenamic acid as antipyretic. Since there are only a few studies comparing efficacy and tolerability of paracetamol, ibuprofen, and mefenamic acid, it was thought prudent to evaluate these three drugs for better efficacy, tolerability, and adverse events in pediatric patients with febrile illness.

Aims and Objectives

The objectives of this study were as follows:

1. To compare the efficacy of paracetamol, ibuprofen, and mefenamic acid
2. To compare the tolerability and adverse effects of paracetamol, ibuprofen, and mefenamic acid.

METHODOLOGY

Study design

Prospective randomized open-label study

Study approval: The study was approved by the Institutional Ethics Committee of Shri B.M. Patil Medical College and Research Centre, Vijayapura

Study site: Pediatric general ward

Study period: 1 year (1-Jan-2018 to 1-Jan-2019).

Source of Data

The sample for the study is febrile pediatric patients admitted in the general ward at Shri B. M. Patil Medical College, Hospital and Research Center, Vijayapura.

Sample Size

With anticipated mean difference of percent reduction in temperature between paracetamol, ibuprofen, and mefenamic acid as 0.81% and anticipated SD as 1.22, the minimum sample size per group is 60 with 90% power and 5% level of significance.

Total 180

By using the formula:

$$n= (z\alpha+z\beta)^2 2\ SD^2$$

MD^2

Where Z=Z statistic at a level of significance

MD=Anticipated mean difference

SD=Anticipated standard deviation.

Inclusion Criteria

The following criteria were included in the study:

1. All children presenting with fever at the time of admission

2. Patients/attenders ready to give informed consent
3. Patients in the age group of 1 month – 14 years.

Exclusion Criteria

The following criteria were excluded from the study:

1. Uncooperative patients
2. Patients not following the protocol
3. Patients who were hypersensitive to drugs
4. Patients who received antipyretics within 6 h preceding study
5. Severely ill patients requiring ICU admission.

Children admitted in the general ward are block randomized into three groups based on the oral antipyretic given and were observed for 24 h.
Group A: Paracetamol at a dose of 15 mg/kg 6 hourly
Group B: Ibuprofen at a dose of 10 mg/kg 6 hourly
Group C: Mefenamic acid at a dose of 8 mg/kg 6 hourly.

The following parameters were recorded in all the groups:

1. Evaluation of efficacy

Axillary temperature was recorded using a Omron® MC 246 Digital.
Thermometer.

The temperature was measured at:

- At the time of admission
- At hourly intervals for first 3 h and then every 6th hourly.

2. Withdrawal of the patient from the study
   - The patient condition deteriorates or becomes severely ill
   - Withdrawal of consent of the parents/guardians.

3. Tolerability evaluation

Modified treatment tolerability evaluation score.[3,4]
Symptoms such as vomiting, dislikeness for meals (nausea), and daytime sleeping were assessed and scores were recorded from 0–3.

- Score 0: Absent–symptom is not present
- Score 1: Mild–symptom is present but is not troublesome
- Score 2: Moderate–symptom is frequently troublesome but would not interfere with daily activity
- Score 3: Severe–symptom is troublesome.

Statistical Analysis

All characteristics were summarized descriptively. For continuous variables, the summary statistics of mean ± SD were used. For categorical data, the number and percentage were used in the data summaries and diagrammatic presentation. Chi-square test was used for the association between two categorical variables. The difference of the means of analysis variables between 2-time points in the same group was tested by paired t-test. The difference of the means of analysis variables between more than two independent groups was tested by ANOVA and F-test of testing of equality of variance. If $P < 0.05$, then the results were considered to be statistically significant; otherwise, it was considered as not statistically significant. Data were analyzed using SPSS software v.23.0. and Microsoft Office 2007.

RESULTS

In our study, we randomized 60 patients to each of the three study groups – oral paracetamol, oral ibuprofen, and oral mefenamic acid. However, a few patients had to be administered the antipyretics intravenously, as shown in Table 2, thereby reducing the actual sample size to that extent.

The number of patients experiencing adverse effects of vomiting, dislikeness for meals, and daytime sleeping among the three study groups is shown in Table 3. Vomiting was reported in the paracetamol group by 11.5% of patients, followed by 5.4% and 5.3% in the ibuprofen and mefenamic acid group, respectively. Dislikeness for meals was reported by 10.5% of patients in the mefenamic acid group, followed by 7.7% of patients in the paracetamol group and 5.4% patients in the ibuprofen group. Daytime sleeping was reported by 5.4% and 5.3 % patients in the ibuprofen and mefenamic acid groups, respectively. In the paracetamol group, none of the patients reported daytime sleeping.

Table 2: Distribution of study groups

Antipyretic	Total sample	IV antipyretic given	Actual sample
Paracetamol	60	8	52
Ibuprofen	60	4	56
Mefenamic acid	60	3	57

Table 3: Distribution of adverse effects between study groups

Adverse effects	Paracetamol		Ibuprofen		Mefenamic acid		*P*-value
	n	%	*N*	%	*n*	%	
Vomiting	6	11.5%	3	5.4%	3	5.3%	0.359
Dislikeness for meals	4	7.7%	3	5.4%	6	10.5%	0.593
Daytime sleeping	0	0.0%	3	5.4%	3	5.3%	0.239

The plot of the patient temperature at different time periods after admission for the three study groups is shown in Figure 1. At the end of 24 h, the maximum fall in temperature is observed in the mefenamic acid group, followed by ibuprofen group and then paracetamol group.

The fall in mean temperature from the baseline at different observation points for the study groups is shown in Table 1 and Figure 2. At the end of 2 h, the fall in mean temperature from the baseline for the mefenamic acid group is maximum (1.85°F) as compared to the other two groups and is statistically significant ($P = 0.028$). Even at the end of 6 h, the fall in mean temperature for mefenamic acid group is more (2.60°F) and is statistically significant (0.028).

DISCUSSION

Fever is not a primary illness but it is a physiological 18 mechanism that has beneficial effects in fighting infection. The increase in body temperature causes discomfort for children. Hence, antipyresis is one of the most usual therapeutic interventions undertaken. Paracetamol and, more recently, ibuprofen are generally used over the counter drugs for antipyresis. However, of late, there is a trend of increased use of mefenamic acid as antipyretic. All three drugs belong to the class of NSAIDs. They inhibit COX-dependent production of prostaglandins which are involved in mediating inflammation, pain, fever, and swelling. We evaluated these three drugs for their antipyretic efficacy and adverse events in pediatric patients with febrile illness. In our study, all three drugs – paracetamol, ibuprofen, and mefenamic acid proved to be effective antipyretic drugs. In the paracetamol group, the mean body temperature decreased from 100.99°F at baseline to 99.28°F at 2 h, while, in the ibuprofen group, it decreased from 100.72 ± 0.47 at baseline to 99.14°F ± 0.48 at 2 h and in the mefenamic acid group from 100.91° F ±0.63 at baseline to 99.16 °F ± 0.54 at 2 h. This decrease in body temperature at 2 h from the mean baseline temperature at admission was statistically significant in the mefenamic acid group ($P = 0.028$). Similarly, at the end of 6 h, the mean body temperature decreased significantly ($P = 0.028$) in the mefenamic acid group. Thus, the onset of action is faster for mefenamic acid group. The efficacy after 6 h is maximum for mefenamic acid as compared to paracetamol and ibuprofen. At the end of 24 h, mefenamic acid group showed a maximum reduction in baseline mean temperature among the three study groups.

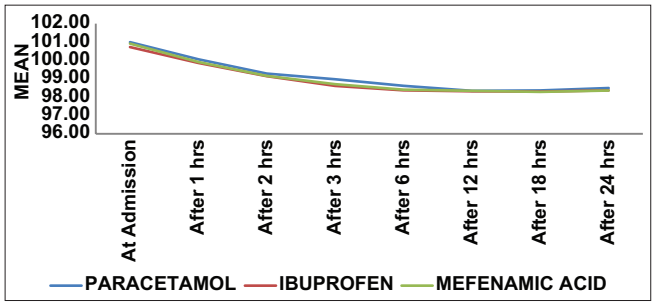

Figure 1: Fall of mean temperature among the study groups

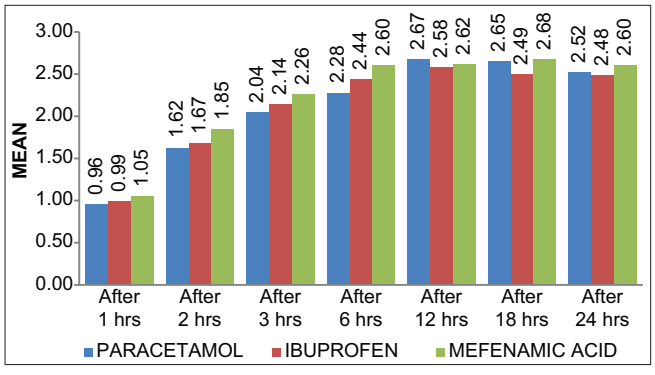

Figure 2: Difference of mean temperature between study groups

Very less data are available on comparative studies between the three drugs – paracetamol, ibuprofen, and mefenamic acid, as compared to data evaluating paracetamol and ibuprofen.

A comparative study between paracetamol suspension (15 mg/kg) and mefenamic acid suspension (4 mg/kg) by Kunkulol *et al.*[2] reported that the fall in temperature at 1 h was more in mefenamic acid group (102.12°F–99.5°F) compared with paracetamol group (101.81°F–100.32°F). At 6 h, the decrease was significantly more in mefenamic acid group as compared with paracetamol group (3.23% vs. 2.47%, $P < 0.01$). This is in line with our results. An Indian study by Khubchandani *et al.*[5] showed that mefenamic acid (6.5 mg/kg) demonstrated significantly better antipyretic activity compared to paracetamol (10 mg/kg) ($P < 0.05$) over the 4 h period of observation and ibuprofen (7 mg/kg) ($P < 0.05$) in the 2–4 h range. Mefenamic acid continued to show antipyretic activity at the end of 4 h in contrast to ibuprofen and paracetamol, but since the period of observation in the study was restricted to 4 h, the study was unable to quantify the precise duration of extended antipyretic efficacy of mefenamic acid. Our study corroborates the same result.

In our study, 11.5%, 5.4%, and 5.3% of patients reported vomiting in the paracetamol, ibuprofen, and mefenamic acid group, respectively. The occurrence of vomiting was not significantly associated with any particular study group ($P = 0.359$). In a study by Kunkulol *et al.*,[2] 6% and 4% of patients in the paracetamol and mefenamic acid group, respectively, reported vomiting, with no significant association with the study group ($P > 0.05$). Dislikeness for

meals was reported by 10.5% of patients in the mefenamic acid group, followed by 7.7% of patients in the paracetamol group and 5.4% of patients in the ibuprofen group in our study. Dislikeness for meals was not significantly associated with any of the study groups ($P = 0.593$). In the study by Kunkulol *et al*.,[2] dislikeness for meals was reported by 10% of patients in the paracetamol group and 14% of patients in the mefenamic acid group, but the association was not significant ($P > 0.05$). In both studies, the mefenamic acid group reported higher dislikeness for meals, though not significant. In our study, daytime sleeping was reported by 5.4% and 5.3% of patients in the ibuprofen and mefenamic acid groups, respectively, while none of the patients in the paracetamol group reported daytime sleeping. Daytime sleeping was not significantly associated with any particular study group ($P = 0.239$). In the study by Kunkulol *et al*.,[2] 4% of patients in the paracetamol and ibuprofen group each reported daytime sleeping, without any significant association ($P > 0.05$).

Thus, in our study, mefenamic acid is found to be a better antipyretic as compared to paracetamol and ibuprofen, providing a faster onset of action and prolonged effect.

CONCLUSION

Mefenamic acid in the doses used in the study was shown to be more effective and well-tolerated than ibuprofen and paracetamol in the treatment of fever in young children. Although the treatment appeared safe, it will require continuing vigilance from those caring for children before mefenamic acid is given the confidence afforded by paracetamol or ibuprofen as antipyretics.

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