Randomized controlled study of the antipyretic efficacy of oral paracetamol, intravenous paracetamol, and intramuscular diclofenac in patients presenting with fever to the emergency department

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Background: Fever is a common problem in adults visiting the emergency department. Extensive studies have been done in children comparing the efficacy of various antipyretics. However, studies on the efficacy of antipyretic drugs in adults are very scarce. To the best of our knowledge, no controlled trial has been carried out comparing the antipyretic efficacy of paracetamol (oral and intravenous) and intramuscular diclofenac in adults.

Methods: In this parallel-group, open-label trial, participants aged 14–75 years presenting with fever who had a temperature of more than 38.5°C were enrolled and treated. Participants were randomly allocated to receive treatment with 1,000 mg oral paracetamol (n = 145), 1,000 mg intravenous paracetamol (n = 139), or 75 mg intramuscular diclofenac (n = 150). The primary outcome was degree of reduction in mean oral temperature at 90 minutes. The efficacy of diclofenac versus oral and intravenous paracetamol was assessed by superiority comparison. Analysis was done using intention to treat principles.

Results: After 90 minutes, all three groups showed a significant reduction in mean temperature, with intramuscular diclofenac showing the greatest reduction (-1.44 ± 0.43 , 95% confidence interval [CI] -1.4 to -2.5) and oral paracetamol the least (-1.08 ± 0.51 , 95% CI -0.99 to -2.2). After 120 minutes, there was a significant difference observed in the mean change from baseline temperature between the three treatment groups ($P < 0.0001$). Significant changes in temperature were observed in favor of intramuscular diclofenac over oral and intravenous paracetamol at each time point from 60 minutes through 120 minutes inclusive.

Conclusion: Both intramuscular diclofenac and intravenous paracetamol showed superior antipyretic activity than oral paracetamol. However, in view of its ease of administration, intramuscular diclofenac can be used as a first-choice antipyretic in febrile adults in the emergency department.

Keywords: antipyretic, intramuscular, intravenous, paracetamol, diclofenac, emergency department

Introduction

Fever accounts for a substantial proportion of adult emergency consultations or visits. It is one of the leading patient complaints aside from abdominal pain and chest pain in all emergency department visits.¹ Although there may be physiologic benefits of fever, it also associated with arthralgia, myalgia, nausea, and vomiting. Treatment with antipyretics improves these accompanying symptoms² and reduces patient discomfort.³

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Both pharmacologic and nonpharmacologic methods like tepid sponging⁴ have been used to reduce body temperature in febrile patients. Extensive studies have been done in children comparing the efficacy of various antipyretics. These have included paracetamol, ibuprofen, nimesulide, ketoprofen, propacetamol, and dipyron. ⁵⁻¹⁹

Studies on the efficacy of antipyretic drugs in adults are very scarce. Most of the available studies on acetaminophen were carried out in endotoxin-induced febrile models²⁰⁻²² and others in intensive care patients.²³ Few studies have been done on oral diclofenac using varying doses²⁴ or comparing it with ibuprofen²⁵ or acetylsalicylic acid.²⁶ Intravenous ketorolac has also been studied as an antipyretic in adults.²⁷ To the best of our knowledge, no controlled trial has been carried out comparing the antipyretic efficacy of paracetamol (both oral and intravenous) and intramuscular diclofenac in adults. Therefore, we decided to compare the antipyretic efficacy of oral and intravenous paracetamol with that of intramuscular diclofenac in febrile adults in the emergency department.

Materials and methods

Study design, participants, and randomization

A randomized controlled clinical trial was conducted in the emergency department at Alkhor Hospital, Hamad Medical Corporation, in the state of Qatar from June 2008 to December 2011. Adults aged 14–75 years were included if they had an oral temperature of more than 38.5°C. A complete clinical assessment including past and present medical history was performed. The main exclusion criteria were a history of allergy to any of the trial medications, antipyretics within the previous 8 hours, renal, hepatic or hematologic disorders, bronchial asthma, peptic ulcer disease, and frequent vomiting. Pregnant or lactating women were also excluded. The study was approved by the local ethics committee at the Medical Research Center, Hamad Medical Corporation (number 9070/09) and was done in accordance with the principles of the Declaration of Helsinki and guidelines for Good Clinical Practice. All patients provided their written informed consent prior to enrollment. The trial is registered with ClinicalTrials.gov (NCT01891435).

The randomization sequence list was created using a computerized random number generator. Participants were assigned to one of the three treatment groups using an equal allocation ratio of 1:1:1. The allocation sequence was concealed from the investigators enrolling the patients in sequentially numbered and sealed envelopes. The corresponding envelopes were opened only after the participants

completed all baseline assessments and it was time to allocate the intervention. Randomization codes were kept secure until all data entry was complete.

Sample size

The primary outcome measure was the mean oral temperature decrease from baseline at 90 minutes. It was assumed that the mean oral temperature decrease for the three treatments was 1.4°C (intramuscular diclofenac), 1.22°C (intravenous paracetamol), and 1.1°C (oral paracetamol), respectively, with a constant standard deviation of 0.5°C for the three treatments. The sample size needed to achieve the desired power of 80% ($\beta = 0.20$) at the 5% ($\alpha = 0.05$) level of significance was 130 patients per treatment group.

Procedures

Baseline oral temperature was recorded at enrollment. Patients were randomly assigned to receive oral paracetamol 1,000 mg, intravenous paracetamol 1,000 mg, or intramuscular diclofenac sodium 75 mg supplied from the hospital pharmacy free of cost to the patients. Intravenous paracetamol was given as an infusion over 15 minutes. Oral temperature was recorded at 30, 60, 90, and 120 minutes after drug administration. All temperature recordings were done using a standard thermometer. The primary outcome was the degree of reduction in mean oral temperature at 90 minutes and the secondary outcome was the degree of reduction in mean oral temperature at 30, 60, and 120 minutes. Patients were also monitored for any adverse effects pertaining to the trial medications.

Statistical analysis

Categorical and continuous values were expressed as the frequency (percentage) and mean $\pm$ standard deviation. Descriptive statistics were used to summarize all demographic and other clinical characteristics of the patients. Baseline participant characteristics in the three groups were compared using one-way analysis of variance (ANOVA) for continuous variables and chi-square tests for categorical variables. For the primary outcome variable, ie, reduction in mean oral temperature at 90 minutes was compared using one-way ANOVA. The results are presented with the associated 95% confidence interval. Where an overall group difference was found to be statistically significant, pairwise comparisons were made using the appropriate post hoc test. Reduction in mean oral temperature at 30, 60, and 120 minutes was analyzed using repeated-measures ANOVA. Means of quantitative variables between two independent groups were analyzed using the unpaired *t*-test. Associations between two or more qualitative

Figure 1 Patient flow and enrollment chart.

Abbreviations: IM, intramuscular; IV, intravenous.

or categoric variables were assessed using the chi-square test. For small cell frequencies, the chi-square test was used with a continuity correction factor. Pictorial presentations of the key results were made using appropriate statistical graphs. A two-sided P -value < 0.05 was considered to be statistically significant. All statistical analyses were done using Statistical

Package for the Social Sciences version 19 software (SPSS Inc., Chicago, IL, USA).

Results

Six hundred patients were screened for study eligibility (Figure 1). Of these, 166 patients could not participate for

Table 1 Baseline demographic and clinical characteristics of enrolled patients

Variables	IM diclofenac (n = 150)	Oral paracetamol (n = 145)	IV paracetamol (n = 139)	Total (n = 434)	P-value
Age (years)	35.5 ± 14.24	36.2 ± 15.35	36.4 ± 14.98	36.1 ± 15.81	0.695
Gender					
Male	150 (100.0%)	144 (99.3)	139 (100.0%)	433 (99.8%)	0.881
Female	0.0 (0.0%)	1 (0.7%)	0.0 (0.0%)	1 (0.2%)	
IV fluids					
Yes	36 (24.0%)	28 (19.3%)	44 (31.7%)	108 (24.9%)	0.054
No	114 (76.0%)	117 (80.7%)	95 (68.3%)	326 (75.1%)	
Antibiotic					
Yes	9 (6.0%)	15 (10.3%)	20 (14.4%)	44 (10.2%)	0.064
No	141 (94.0%)	130 (89.7%)	119 (85.6%)	389 (89.8%)	
Nationality					
Indian	45 (30.0%)	60 (41.4%)	46 (33.1%)	151 (34.8%)	0.238
Nepalese	68 (45.3%)	49 (33.8%)	51 (36.7%)	168 (38.7%)	
Pakistani	10 (6.7%)	8 (5.5%)	16 (11.5%)	34 (7.8%)	
Bangladeshi	12 (8.0%)	10 (6.9%)	9 (6.5%)	31 (7.1%)	
Sri Lankan	11 (7.3%)	8 (5.5%)	9 (6.5%)	28 (6.5%)	
Others	4 (2.7%)	10 (6.9%)	8 (5.8%)	22 (5.1%)	

Abbreviations: IV, intravenous; IM, intramuscular.

Table 2 Comparison of mean temperature at different time points between the three treatment groups

Time (minutes)	IM diclofenac			Oral paracetamol			IV paracetamol			P-value
	n	Mean	SD	n	Mean	SD	n	Mean	SD	
0	150	39.27	0.438	145	39.28	0.473	139	39.38	0.527	0.112
30	150	38.88	0.421	145	39.04	0.526	139	38.92	0.463	0.009
60	150	38.28	0.394	145	38.59	0.487	139	38.37	0.424	<0.0001
90	143	37.84	0.407	142	38.21	0.542	137	38.03	0.443	<0.0001
120	112	37.55	0.387	118	38.00	0.436	118	37.80	0.436	<0.0001

Note: Number of patients, particularly at 90 and 120 minutes, are less because patients who had temperatures within the normal range recovered and were discharged from hospital.

Abbreviations: IV, intravenous; IM, intramuscular; SD, standard deviation.

various reasons (140 did not fulfill the inclusion criteria or met an exclusion criterion and 26 did not give their consent to participate in the trial). Therefore, a total of 434 adults were enrolled, randomized, and received the study medications, ie, oral paracetamol ($n = 145$), intravenous paracetamol ($n = 139$), and intramuscular diclofenac ($n = 150$). Baseline demographic and clinical characteristics were similar across the three treatment groups ($P > 0.05$, Table 1). The majority of the study subjects enrolled were males. This can be attributed to the location of the hospital, which caters mainly for the migrant labor community of the surrounding industrial area. The mean patient age was 36.1 ± 15.81 years. Mean oral temperature at baseline was similar across the three treatment groups. Figure 1 shows the enrollment of participants through each stage of the trial.

After 90 minutes, all three groups showed a significant reduction in mean temperature, with intramuscular diclofenac showing the greatest (-1.44 ± 0.43 , 95% confidence interval [CI] -1.4 to -2.5) and oral paracetamol the least (-1.08 ± 0.51 , 95% CI -0.99 to -2.2). After 120 minutes, there was a significant difference observed in the mean change from baseline temperatures between the three treatment groups ($P < 0.0001$). Significant changes in temperature were observed in favor of intramuscular diclofenac over oral and intravenous paracetamol at each time point from 60 minutes through 120 minutes inclusive (Table 3). Repeated-measures ANOVA revealed a significant reduction in the change from mean baseline temperature within each treatment group, particularly at 60, 90, and 120 minutes (Table 2 and Figure 2). Patients who received intravenous fluids showed a significantly higher reduction in mean temperature from baseline, particularly at 30 minutes (-0.45 ± 0.38 versus -0.33 ± 0.34 ; $P = 0.002$) and 120 minute (-1.7 ± 0.59 versus -1.5 ± 0.51 ; $P = 0.030$). Reduction in mean temperature at the various time points was not significantly different among patients receiving antibiotics.

Discussion

Fever occurs as a response to a variety of infectious and non-infectious inflammatory conditions. It is due to abnormally high hypothalamic thermostasis caused by the actions of interleukin or pyrogenic cytokines on the hypothalamic thermoregulatory center. Although treating the underlying cause should be the primary objective, reducing the fever is also important because this decreases constitutional symptoms and the discomfort to the patient.

We believe that this is the first study to compare directly the antipyretic efficacy of intramuscular diclofenac and paracetamol (both oral and intravenous), which are the two drugs commonly used in adults. Our results are in partial agreement with the findings of a previous study done by Peacock et al²⁰ comparing intravenous and oral paracetamol, which showed a statistically significant difference in temperature in the first 2 hours favoring intravenous over oral acetaminophen. Similarly, another study done by Kett et al²¹ showed a significant reduction in temperature at 30 minutes from baseline by intravenous acetaminophen 1,000 mg in comparison with placebo. However, both these studies were done using endotoxin-induced febrile models. Another study done in an endotoxin-induced model showed oral acetaminophen to have a greater effect than aspirin.²²

Figure 2 Mean temperatures at different time points for the three treatment groups. **Abbreviation:** IV, intravenous.

Table 3 Between-treatment comparisons of mean change from baseline in temperatures at different time points

Time/temperature (minutes)	IM diclofenac Mean $\pm$ SD (95% CI)	Oral paracetamol Mean $\pm$ SD (95% CI)	IV paracetamol Mean $\pm$ SD (95% CI)	P-value
30	-0.39 $\pm$ 0.29 (-0.34, -1.5)	-0.45 $\pm$ 0.36 (-0.39, -1.7)	-0.23 $\pm$ 0.35 (-0.17, -2.5)	<0.0001
60	-0.99 $\pm$ 0.34 (-0.94, -2.1)	-0.69 $\pm$ 0.43 (-0.61, -1.7)	-1.01 $\pm$ 0.40 (-0.94, -2.2)	<0.0001
90	-1.44 $\pm$ 0.43 (-1.4, -2.5)	-1.08 $\pm$ 0.51 (-0.99, -2.2)	-1.35 $\pm$ 0.46 (-1.3, -3.1)	<0.0001
120	-1.81 $\pm$ 0.46 (-1.7, -2.9)	-1.35 $\pm$ 0.51 (-1.3, -2.5)	-1.63 $\pm$ 0.55 (-1.5, -4.1)	<0.0001

Note: Mean change from baseline = post baseline mean – baseline mean 95% CI for mean change from baseline.

Abbreviations: IV, intravenous; IM, intramuscular; SD, standard deviation; CI, confidence interval.

Gehanno et al compared the antipyretic and analgesic effects of oral paracetamol with that of various doses of oral diclofenac. They found that diclofenac at doses of 12.5 mg and 25 mg had a greater analgesic and antipyretic effect than paracetamol.²⁴

There has been no study done on the antipyretic effect of intramuscular diclofenac. However, a study comparing three intravenous antipyretics, ie, diclofenac 75 mg, metamizole 2,500 mg or 1,000 mg, and propacetamol 2,000 mg or 1,000 mg in hematology/oncology patients found metamizole to be the most effective, while propacetamol 1,000 mg had the least antipyretic efficacy. However, major drawbacks of this study are that it was nonrandomized and done in cancer patients.² The limitation of our study is that the majority of the subjects enrolled were males. This can be attributed to the location of the hospital which mainly caters for the migrant labor community in the surrounding industrial area.

Conclusion

In this study, intramuscular diclofenac and intravenous paracetamol were more effective in achieving a significant reduction in temperature at each time point from 60 minutes through 120 minutes inclusive. Of the two agents, intramuscular diclofenac showed the greatest effect. Beyond 90 minutes, all three drugs showed significant antipyretic activity, with oral paracetamol having the least effect and intramuscular diclofenac having the greatest effect. Hence we conclude that, in the emergency department, intramuscular diclofenac can be used as an antipyretic of choice to reduce temperature within a short time. However, if rapid reduction is not required, patients can be treated with oral paracetamol.

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Disclosure

The authors report no conflicts of interest in this work.

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