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Research Article

IV VS ORAL PARACETAMOL FOR FEVER IN HOSPITALIZED CHILDREN: IS IV PARACETAMOL SUPERIOR TO ORAL PARACETAMOL AS ANTIPYRETIC?

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ABSTRACT
*Introduction***:** Fever is one of the commonest symptoms in children visiting medical care. Paracetamol is the most widely used drug for reducing fever in children. By randomized control trial, we wanted to compare IV and oral Paracetamol for their antipyretic effectiveness in hospitalised children. *Methodology*: Randomized control trial was done in pediatric department of tertiary care hospital of rural Bangalore over period of 2 years from 2017 to 2019. Children less than 5 years, admitted with fever and having temperature more than 100 ^{0}F,were allotted into one of the two groups of Paracetamol administration i.e. oral and IV after written informed consent. Calculated dose of Paracetamol (15 mg/kg/dose for oral and 10 mg/kg/dose for IV) was administered by the respective route. Axillary temperature was measured at baseline, after 30 minutes ,60 minutes and hourly thereafter till 6 hours and documented. Subjects were monitored for adverse events. *Results***:** 100 children were enrolled in the study and allotted as 50 each in oral and IV Paracetamol study groups. The mean fall in temperature at 1 hour after IV Paracetamol was 2.63 degree F and after oral Paracetamol was 1.51 degree F, with significant statistical difference. At 4 hour and 6 hour, mean temperature observed following administration of Paracetamol via both the routes did not show any significant statistical difference indication rapid onset of action of IV Paracetamol compared to oral but similar antipyretic effectiveness at 4 and 6 hours. There were no adverse events observed. *Conclusions:* Oral and IV Paracetamol are effective antipyretics. IV Paracetamol can be preferred when rapid onset of action is needed or when oral route is not possible or contraindicated.

Keywords*: Antipyretics, Children, Intravenous, Paracetamol, Oral*

INTRODUCTION
Fever is one of the commonest symptoms in children visiting medical care.(Lorin *et al,* 2004); Tréluyer *et al.,* 2001). Fever causes significant anxiety and apprehensions among parents. Antipyretics administration and tapid sponging forms the mainstay of fever reduction.
Various antipyretics are used by practitioner or parents themselves, as on need basis for fever. Paracetamol, Ibuprofen, Mefenamic acid are commonly used antipyretics. Among the antipyretics available, Paracetamol is the most widely used drug for reducing fever in children .(Lorin *et al,* 2004; Tréluyer *et al.,* 2001; .Keith *et al.,* 2007; Wong *et al.,* 2001) It is found to be safe in standard doses of 10-15 mg/kg/dose 6hourly (maximum 60 mg/kg/day) (Lorin *et al,* 2004; Wong *et al.,* 2001; Jenson *et al,* 2006). Most common route of administration is oral, but can be administered rectally or intravenously. Administration of oral medication in young children can sometimes be time consuming, with 1 in 7 children vomiting up medication within 20 minutes (Prado *et al.,* 2006) Other routes of administration like rectal and IV administration need to be used in that settings.
In hospital settings, where any of the routes can be used for fever reduction, commonly intravenous route is preferred over oral route in case of high grade of fever or when rapid decrease in fever is intended. Few studies have found Intravenous route most rapid and more efficient than oral route (Kumpulainen *et al.,* 2007). Intravenous route has its own complications such as risk of allergic reactions and risk of thrombophlebitis. Therefore, when both the routes of administration can be used in hospital settings, we

want to compare the antipyretic effectiveness of the standard doses of Paracetamol administered orally and intravenously.

Objectives of the study:

1. To compare the antipyretic effectiveness of oral and intravenous Paracetamol.
2. To study the side effects of Paracetamol by these routes.

MATERIALS AND METHODS

Type of study: Randomized control trial

Source of data: Patients admitted in paediatric ward and paediatric Intensive Care Unit of MVJ medical college and research Hospital Hoskote, meeting the inclusion criteria were included. Ethical clearance was taken from ethical and scientific research committee of the institute.

*Inclusion Criteria***:** Febrile children within age group of 30 days to 5 years, admitted in paediatric Intensive Care or Paediatric Ward, having axillary temperature of ≥100 °F were approached for enrolment in the study.

*Exclusion criteria***:** Children with diminished level of consciousness, known allergy to Paracetamol, shock, respiratory distress, active seizures, diarrhoea in the previous 24 hours, history of other antipyretic drugs in previous 6 hours.

Computer-generated random table chart was used for randomization. Subjects were assigned to Oral or IV Paracetamol group after written informed consent. In the first group received 15 mg/kg Paracetamol Orally, the second group received 10 mg/kg Paracetamol intravenously. After enrolment in one of the study groups, demographic data, duration of fever along with provisional diagnosis was recorded. Baseline axillary temperature was measured with digital thermometer by resident doctor and was recorded. Depending on subject's weight, required dose of Paracetamol was calculated to the nearest round off dose. The calculated nearest weight-based dose of Paracetamol either orally or IV was administered by nurse. For oral route, syrup containing 120 mg/5mL, 250mg/5ml or tablets of 500mg/650mg strength of Paracetamol was used. The dose was calculated in mg and is then converted to mL. The required dose is given by a calibrated sterile syringe. For intravenous route, calculated dose was given as infusion over 15 to 20 minutes. Subsequently, axillary temperature will be recorded after 30 minutes and then hourly till 6 hours. All the subjects were monitored for possible adverse effects of administered Paracetamol and if present were noted down.

*Statistical analysis***:**

Data was entered into Microsoft excel data sheet and was analyzed using SPSS 22 version software. Categorical data was represented in the form of Frequencies and proportions. Chi-square test was used as test of significance for qualitative data. Continuous data was represented as mean and standard deviation. P value (Probability that the result is true) of <0.05 was considered as statistically significant after assuming all the rules of statistical tests. MS Excel**,** SPSS version 22 **(**IBM SPSS Statistics, Somers NY, USA) was used to analyze data.

RESULTS

100 subjects were included in the study after written informed consent. By computer generated randomized chart, out of those 100 patients, 50 were allotted in oral and 50 in IV Paracetamol group.

Out of 100 subjects, 12(12%) patients were in age group of less than 1year of age, 27(27%) patients were in 1 to 2 years of age group and maximum i.e. 61(61%) were in 3 to 5years of age group (P value:0.43). Age distribution of patients in different study groups represented in table 1.

Table 1: Age Distribution of patients with respect to routes of administration

Age group	Oral		IV	
	N	%	N	%
<1year	8	16.0%	4	8.0%
1 to 2 year	12	24.0%	15	30.0%
3 to 5 years	30	60.0%	31	62.0%

Oral and IV groups had 16% and 8% of the patients respectively in less than 1 year age group. 24% and 30% in age group of 1 to 2 years, and 60%, 62 % in 3 to 5 years age group respectively. Majority of patients were in age group of 3-5 years in both the study groups.
There was no significant statistical difference in age distribution among these study groups.
Out of 100 patients, 40 were females and 60 were males.
Gender distribution of patients in study groups is shown in table 2

Table 2: Gender distribution in both study groups.

Gender	Oral		IV	
	N	%	n	%
Female	19	38	21	42
Male	31	62	29	58
Total	50	100	50	100

In oral group, 62% were males and 38% were females. In IV group, 58% were males and 42% were females. There was no significant statistical difference with regard to gender in oral and IV groups.
Duration of fever in different study groups is shown in table 3

Table 3: Duration of Fever comparison with respect to route of administration

Duration of fever	Oral		IV	
	N	%	N	%
<2 days	25	50	18	36
3 to 5 days	22	44	31	62
> 5 days	3	6	1	2

In oral and IV group, 50% and 36% of patients respectively had < 2 days of fever, 44% and 62% had 3-5 days of fever and, 6% and 2% had >5days of fever respectively. There was no significant difference in duration of fever among both groups. Mean base line temperature of patients in study groups is shown in table 4

Table 4: Mean baseline temperature of Subjects.

Baseline temperature	Oral		IV	
	Mean	SD	Mean	SD
	101.41	1.00	101.13	0.80

Mean baseline temperature in oral, IV groups were 101.41 and 101.13 degree Fahrenheit respectively, with (P value 0.197). Hence, there was no significant difference in mean temperature among all these study groups.Mean temperature following IV & oral Paracetamol is shown in table 5.

Table 5: Mean temperature following IV & oral Paracetamol

TEMPERATURE	Route of administration				P value
	Intravenous		Oral		
	Mean	SD	Mean	SD	
Base Line	101.13	0.80	101.41	1.00	0.115
1HR	98.5	0.71	99.9	1.25	<0.001*
4HR	98.4	0.80	98.5	1.17	0.606
6HR	97.9	0.91	98.3	1.38	0.065

Mean temperature one hour after IV and oral Paracetamol were 98.5 and 99.9 degree F with p value <0.001. Mean temperature after 4 hours & 6 hours of IV and oral Paracetamol were 98.4, 98.5 & 97.9, 98.3 degree F respectively with P value 0.606 & 0.065

There is statistical significant difference in temperature reduced after IV Paracetamol compared to oral Paracetamol at 1 hour, but there is no statistically significant difference at 4 and 6 hours. This suggest rapid onset of action of IV Paracetamol compared to oral Paracetamol. However, overall effectiveness in achieving normal temperature after 4 hours is same in both study groups.

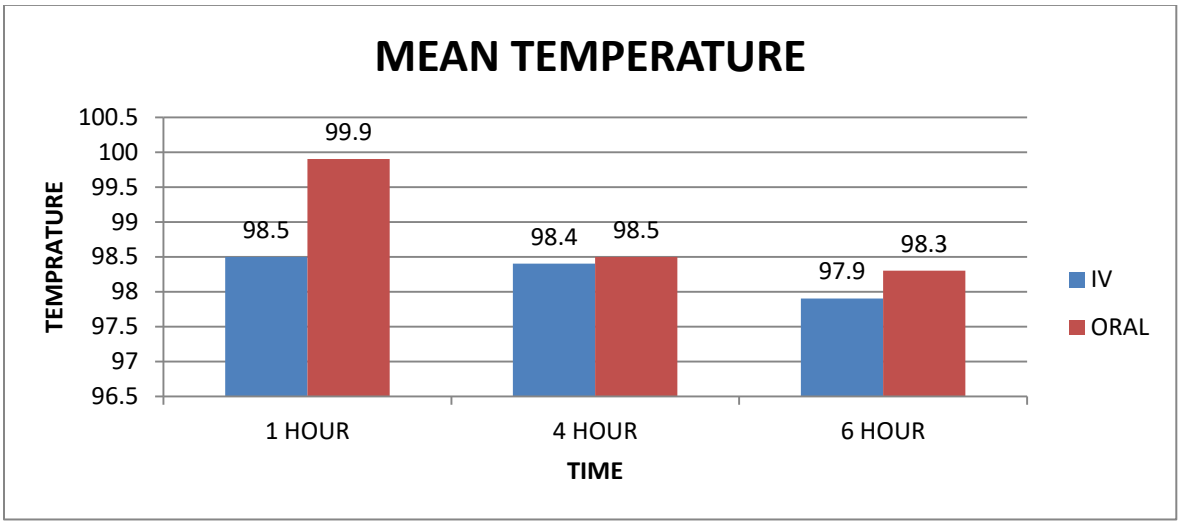

Figure 1: Showing temperature drop in IV and Oral group at 1 hour, 4 hours and 6 hours.

Requirement of additional dose of antipyretic within 6 hours of dose of Paracetamol in study groups in shown in table 6.

Table 6: Readministration of antipyretic in the study groups

Readministration	Oral		IV	
	n	%	n	%
NO	44	88	47	94
YES	6	12	3	6

Out of 100 patients, 6 patients in oral group and 3 patients in IV group required administration of additional dose of antipyretics within 6 hours of dose of Paracetamol by allotted route of administration. Requirement of readministration was quiet less in IV group compared to oral group. The difference was not significant statistically (p=0.48).
In the present study, none of the child in any of the study groups had any significant adverse event such as allergic reactions, hypothermia, vomiting or any other .Also; there was no issue with acceptability of oral and IV route of Paracetamol in any of the child.

DISCUSSION

Fever is a common symptom in children and Paracetamol is the commonest drug used for fever in children for improving the overall comfort and allaying parental anxiety. There is still controversy regarding the comparative antipyretic effectiveness of different routes of administration of Paracetamol. So in the present study, we compared the onset of action and overall effectiveness of oral and IV Paracetamol.
In the present study, 100 children were enrolled in the study. They were allotted as 50 each in oral and IV Paracetamol study groups. There was no significant statistical difference with regard to age ,gender distribution and duration of fever in oral and IV study group. Both study groups were compatible with regard to age, sex and duration of fever. Majority of patients in all the three study groups had duration of fever between 3 to 5 days. This could be because most of the patients approach hospital after one or two days of persistent fever. There was no significant statistical difference in the 3 study groups in relation to the duration of fever.
In the present study, mean baseline temperature in oral and IV was 101.41, 101.13 degree Fahrenheit respectively, with P value 0.197. Hence, there was no significant difference in mean baseline temperature among both study groups.
Mean reduction of temperature one hour following Paracetamol administration:
In our study**,** mean temperature at 1hr following administration of Paracetamol through IV and oral route were 98.5 and 99.9% respectively with p value <0.001 . The mean fall in temperature at 1 hour after IV Paracetamol was 2.63 degree F and after oral Paracetamol was 1.51 degree F suggesting rapid onset of action by IV route compared to oral route. Faster onset of action in intravenous Paracetamol is probably due to its pharmacokinetic advantages including higher bioavailability, faster target plasma concentrations and avoidance of hepatic first pass metabolism. This suggests intravenous route of Paracetamol can be preferred in conditions where rapid reduction of fever is intended for i.e. in children with active seizures, raised intracranial tension, children with respiratory distress with increased oxygen requirements.
Study done by (Roy *et al.,* 2018) revealed that intravenous Paracetamol brought a faster reduction of temperature as compared to oral Paracetamol[51]. Statistically significant difference in the weighed sum of temperature difference through 180 min (P value<0.04) was seen in favour of the intravenous compared to oral.
Kumpulainen E studied CSF penetration of IV Paracetamol and found Paracetamol in CSF as early as at 5 mins after IV administration and highest levels at 57 mins and concluded that the fast and extensive

transfer enables the rapid central analgesic and antipyretic action of IV Paracetamol (Kumpulainen *et al.,* 2007).

Peacock *et al.,* (2011) also found significant changes in the temperature in favour of IV Paracetamol over oral at each time point from T30 through T90.

Mean reduction of temperature four and six hour following Paracetamol administration;

In our study , mean temperature after 4 hours & 6 hours of administration of Paracetamol through IV and oral route were 98.4 , 98.5 degree F and 97.9 , 98.3 degree F respectively. Hence, at 4 hour and 6 hour, mean temperature observed following administration of Paracetamol via both routes did not show any significant statistical difference. Similar to our study done by Roy *et al.,* (2018) Comparing IV and oral Paracetamol antipyretic effectiveness, found that the temperature observed at the end of 6 hour was almost similar in both IV and oral group[51] this suggest that although IV Paracetamol has rapid onset of action compared to oral, overall effectiveness in achieving normal temperature as same.

In our study**,** 6(12%) in oral group, 3 (6%) in IV group required readministration of other dose of antipyretic within 6 hours. Requirement of additional antipyretic dose of IV Paracetamol was less compared to the oral but the difference was not statistically significant.(p= 0.283)

In (Roy *et al., 2018)* study, additional dose of Paracetamol was required in 10 patients (5%) and in 6 patients (3%) in oral Paracetamol group and IV Paracetamol group respectively. Although more patients required in oral group compared to IV , the difference was not significant.

We studied the incidence of side effects of Paracetamol such as hypothermia, allergic reactions, constipation. We did not observe any of these side effects in any of the study group. However study done by (Roy *et al., 2018)* found allergic reaction (rash, itching) in seven patients in IV Paracetamol group. Onset of constipation and dry mouth was also found in 8 patients (4%) in IV Paracetamol group. They did not observe any side effects in oral Paracetamol group.

Limitations of our study

Blinding was not done while randomizing as well as analyzing the results. Children requiring readministration of antipyretics should have been excluded as it would have effect on final outcome. However, the children requiring readministration were quite less. The additional dose of antipyretic was given mostly after 4 hours of study dose of Paracetamol. Its overall impact on results may not be significant.

CONCLUSION

Both IV and oral Paracetamol are effective antipyretics. As IV Paracetamol as rapid onset of action compared to oral, IV Paracetamol can be preferred over oral in patients where rapid reduction of temperature is intended, such as children with seizures, raised intra cranial tension, respiratory distress with increased oxygen demands etc.

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