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# Efficacy of Intravenous Acetaminophen Compared to Oral Acetaminophen for the Management of Fever in Children

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## Abstract

Human body temperature is controlled by the hypothalamus. Neurons in both the preoptic anterior hypothalamus and the posterior hypothalamus receive two kinds of signals: one from peripheral nerves that transmit information from warmth/cold receptors in the skin and the other from the temperature of the blood bathing the region. These two types of signals are integrated by the thermoregulatory center of the hypothalamus to maintain normal temperature. In a neutral temperature environment, the metabolic rate of humans produces more heat than is necessary to maintain the core body temperature in the range of 36.5â??”37.5°C (97.7â??”99.5°F). A normal body temperature is maintained ordinarily, despite environmental variations, because the hypothalamic thermoregulatory center balances the excess heat production derived from metabolic activity in muscle and the liver with heat dissipation from the skin and lungs.[1]

***Index terms—***

## 1 Introduction

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Fever is one of the commonest presenting symptoms in clinical medicine in all age group patients. It is defined as oral temperature of >37.2°C (>98.9°F) in the morning or >37.7°C (>99.9°F) in the evening. **??**1] Fever can be caused by a numerous ailments ranging from potentially serious conditions to very benign illness. This includes both infectious as well as non infectious cause. Infectios illness includes different viral, bacterial and parasitic infections (eg-common cold, urinary tract infections, meningitis, malaria, appendicitis etc). Non-infectious causes include vasculitis, deep vein thrombosis, allergic manifestation, malignancies etc.

Author: e-mail: kumar.drshailendra16@gmail.com Fever may be useful as a defense mechanism as the body's immune response can be strengthened at higher temperatures; however, this issue is controversial.

Fever accounts for a substantial proportion of emergency consultations. It is one of the leading patient complaints aside from abdominal pain and chest pain in all emergency department visits. Treatment with antipyretics not only reduces fever but also improves the associated other symptoms (eg-arthalgia, myalgia,

headache, nausea, vomiting. ??2, ??] It also causes undue worry among the anxious parents of sick kids. Hence treatments of fever with proper antipyeretic medications are extremely important. Antipyretic medications such as ibuprofen or paracetamol are effective at lowering the temperature, which may improve comfort.

Both pharmacologic and nonpharmacologic methods like tepid sponging ??4] have been used to reduce body temperature in febrile patients. Extensive studies have been done in children comparing the efficacy of various antipyretics including paracetamol, ibuprofen, nimesulide, ketoprofen, propacetamol, and dipyrone.

Acetaminophen is a synthetic, nonopioid, centrally acting analgesic and antipyretic agent. ??5] It has a well-established efficacy profile, a well-understood risk?benefit ratio, and a very low potential for harmful drug-drug interactions. ??6] In recommended doses, acetaminophen is considered safe for infants, children, and adults. Although the exact site and mechanism of action of acetaminophen are not clearly defined, its effectiveness as an antipyretic agent has been attributed to its effect on the hypothalamic heat-regulating center ??7, ??, ??] . Worldwide, acetaminophen is currently the most widely used analgesic and antipyretic. Per Oral (PO) acetaminophen was initially approved by the U.S. Food and Drug Administration (FDA) in 1951 and was first marketed in the United States in 1953. Acetaminophen has been well known as an effective analgesic and antipyretic. Intravenous (IV) acetaminophen is approved for the short-term treatment of acute pain and fever in approximately 80 countries outside of the United States and was first approved in Europe in 2001.

Studies on the efficacy of antipyretic drugs are very scarce. Most of the available studies on acetaminophen were carried out in endotoxin-induced febrile models ??10, ??1, ??2] and in intensive care patients. ??13] Few studies have been done on oral diclofenac using varying doses ??14] or comparing it with ibuprofen ??15] or acetylsalicylic acid. Intravenous ketorolac has also been studied as an antipyretic in adults. ??16] To the best of our knowledge, there is very few literature available for comparing the antipyretic efficacy of paracetamol (both oral and intravenous) in children. Therefore, we decided to compare the antipyretic efficacy of oral and intravenous paracetamol in febrile children.

# 2 II.

# 3 Aim and Objectives a) Aim

To determine efficacy of Intravenous Acetaminophen Compared to Oral Acetaminophen for the management of Fever in children.

# 4 b) Formulation of hypothesis

The use of Intravenous Acetaminophen Compared to Oral Acetaminophen for the Management of Fever in children has: a. Better efficacy and tolerability of the Intravenous preparation.

# 5 A) Primary outcome

The primary efficacy outcome will be the weighted sum of temperature differences from baseline at time T 0 through T 360 minutes.

# 6 B) Secondary outcomes

To assess tolerability of oral preparation as compared to intravenous preparation e.g. new onset constipation, allergic reaction and dry mouth.

# 7 III.

# 8 Materials and Methods

# 9 d) Sample size

Based on the statistical calculation a total number of 200 cases were included in the study population in Army Hospital (Research & Referral), Delhi Cantt, India, a tertiary care hospital over one and half years from October 2013 to April 2015.

# 10 e) Inclusion Criteria

All admitted or out-patient department cases with fever more than 103 0 F.

# 11 f) Exclusion Criteria 1) Treated with any other medication having antipyretic

effects within 2 days of admission. 2) Known hypersensitivity to acetaminophen or other NSAIDs. 3) Impaired liver function, active hepatic disease, or evidence of clinically significant liver and renal disease.

g) Methodology 1. All pediatric cases between 1-12 years age, admitted to the Pediatric ward of Army Hospital (R&R), and those presenting to the Pediatric OPD with fever more than 103°F requiring IV/Oral acetaminophen

were considered eligible for the study. 2. Written Informed consent was taken from parents before enrollment in the study and administration of the medicine. 3. Following receipt of consent, children were randomly allocated (using computer generated randomization) in two groups -one group receiving oral PCM and the other one receiving IV PCM divided into two groups alternaone group receiving oral acetaminophen (@15mg/kg/dose) or and the other group receiving IV acetaminophen (@15mg/ kg/dose) as antipyretic. Children were enrolled in each group consecutively. 4. Baseline vital parameters including mean arterial pressure using non-invasive blood pressure monitor by oscillometric technique were recorded. 5. Following administration of the drug the child was monitored for the primary efficacy outcome. 6. Axillary temp. was recorded with mercury thermometer for 5 min every ½ hrly, till 6 hrs. 7. Child was monitored for any evidence of intolerance. 8. All data including the primary and secondary outcomes was recorded as per the Performa.

# 12 h) Ethical Consideration

We have obtained the necessary approval to conduct the study from the Institutional Ethics Committee of Army Hospital (Research and Referral) Delhi Cantt., India. The participants were given a full explanation about the purpose of the study and assurance about the confidentiality of the information and that the participation was optional. Consent of the parents of children was taken prior to enrolment to the study.

# 13 i) Statistical Analysis

All the statistical analysis was performed using SPSS version 20. The clinical profile of patients was analyzed by chi-square test for qualitative variables and Student t test for quantitative variables. 5% probability level was considered as statistically significant i.e., $p<0.05$.

# 14 j) Statement of Limitation

Time to a temperature reduction analysis; time to the specific event (e.g., time to specific temperature or rescue) estimated based on the Kaplan-Meier method (censored at 360 minutes if a subject did not achieve the specified temperature reduction); global evaluation at T 360 minutes summarized for each group by frequency and percentage for each categorical response and analyzed using unstratified Cochran-Mantel-Haenzel mean score test using integer scores; and continuous variables such as change in temperature, maximum temperature reduction, and percentage of subjects with a temperature of <38.5°C, analysis should have carried out for other efficacy endpoints.

# 15 Flow Diagram of Patient Enrolment and Assessment

IV.

# 16 Results

The present study, carried out over a period of one and half years-from October 2013 to April 2015, was aimed at "Efficacy of Intravenous Acetaminophen

# 17 Gender distribution

# 18 Summary and Conclusion

Acetaminophen has been a cornerstone of the management of mild to moderate pain and the treatment of fever for more than 50 years. An intravenous (IV) preparation would allow for rapid, reliable drug delivery to patients in the immediate post-operative setting or in cases where enteral administration is not possible due to underlying disease. The purpose of this study was to assess the dynamics of the onset of antipyretic efficacy of intravenous (IV) acetaminophen versus oral (PO) acetaminophen in the management of fever in children.

This observational single-dose study was conducted at Department of Pedriatrics, Army Hospital (Research and Referral), a multispecialty tertiary care center in New Delhi in fever patients to assess the antipyretic efficacy of IV acetaminophen 15mg/kg/dose versus PO acetaminophen 15mg/kg/dose over 6 hours. Subjects were randomly assigned to receive either IV acetaminophen (n = 100) or PO acetaminophen (n = 100). The salient observations of this study are as follows:

? A total of 200 participants were enrolled, allocated groups and received study medication: 100 in the IV group and 100 in the PO acetaminophen group. ? Demographics and baseline characteristics were similar between the two groups and were normally distributed. ? The mean (±SD) age was 6.7 (±2.75) years, the mean weight was 23.3 (± 6.41) kg. ? The majority of subjects were male (71%). The sex distribution was similar in both the groups 70% males and 30% females. ? Allergic reaction was found in 7 (3.5%) patients in IV acetaminophen group and was absent in PO acetaminophen group [table 8, figure 8]. This association is found to be statistically significant (P value 0.007). ? Onset of constipation and dry mouth was found in 8 patients (4%) in IV acetaminophen group and was absent in PO acetaminophen group [table 10 & 11, figure 10 & 11]. This association is found to be statistically significant (P value 0.004). ? Additional dose was required in 06 patients (3%) in Intravenous acetaminophen group and 10 patients (5%) in Oral Acetaminophen group respectively. However this association

is not statistically significant (P value 0.297). ? Temperature was decreased in all patients in both the Intravenous and Oral acetaminophen groups except some had required some extra additional dose. ? Statistically significant differences in the WSTD through 180 minutes ($p < 0.004$) were observed in favor of the IV acetaminophen group when compared to those receiving PO acetaminophen. After 4 hours, there was no difference in the WSTD between the treatment groups. ? Significant changes in temperature were observed in favor of IV acetaminophen over PO at each time point from T0 through T180.

From the results of the present study, it may be concluded that a single dose of intravenous acetaminophen is safe and effective in reducing fever. Intravenous acetaminophen may be useful where patients are unable to tolerate oral administration or when rapid reduction of temperature is desirable.

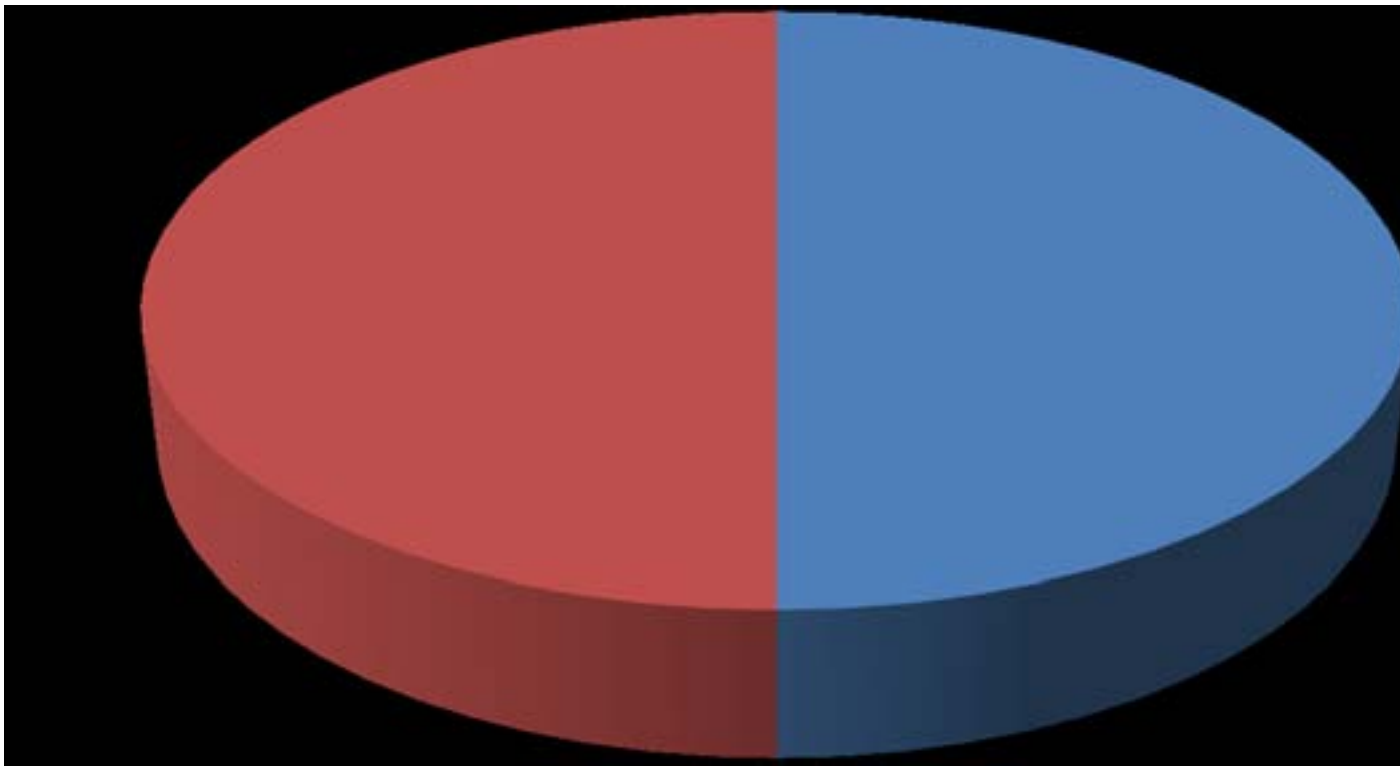

Figure 1:

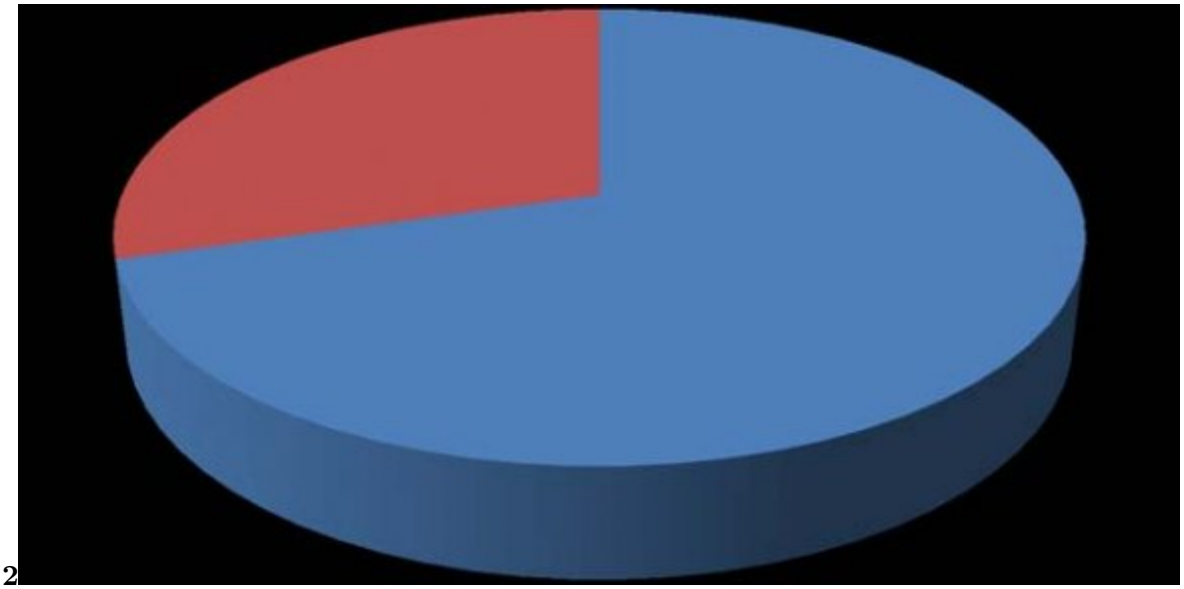

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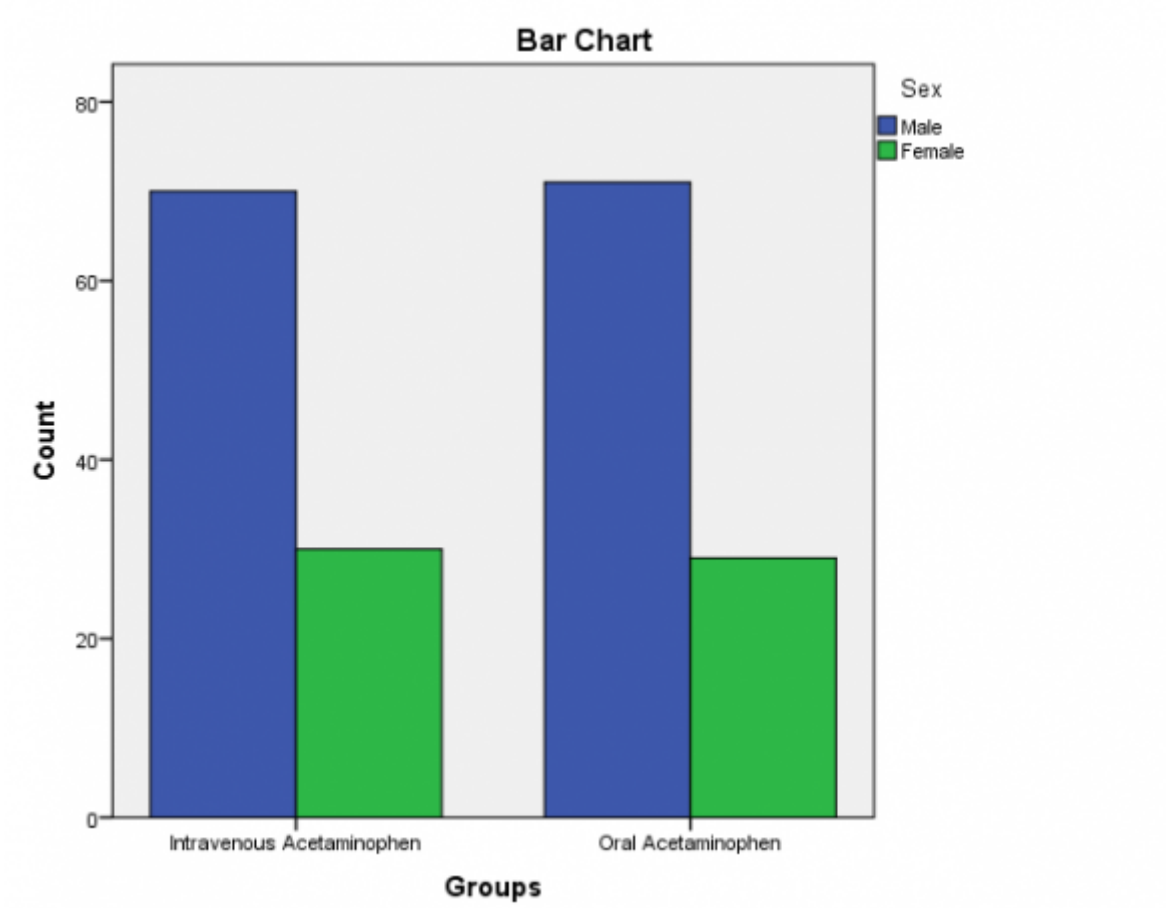
Figure 2: Figure 2 :

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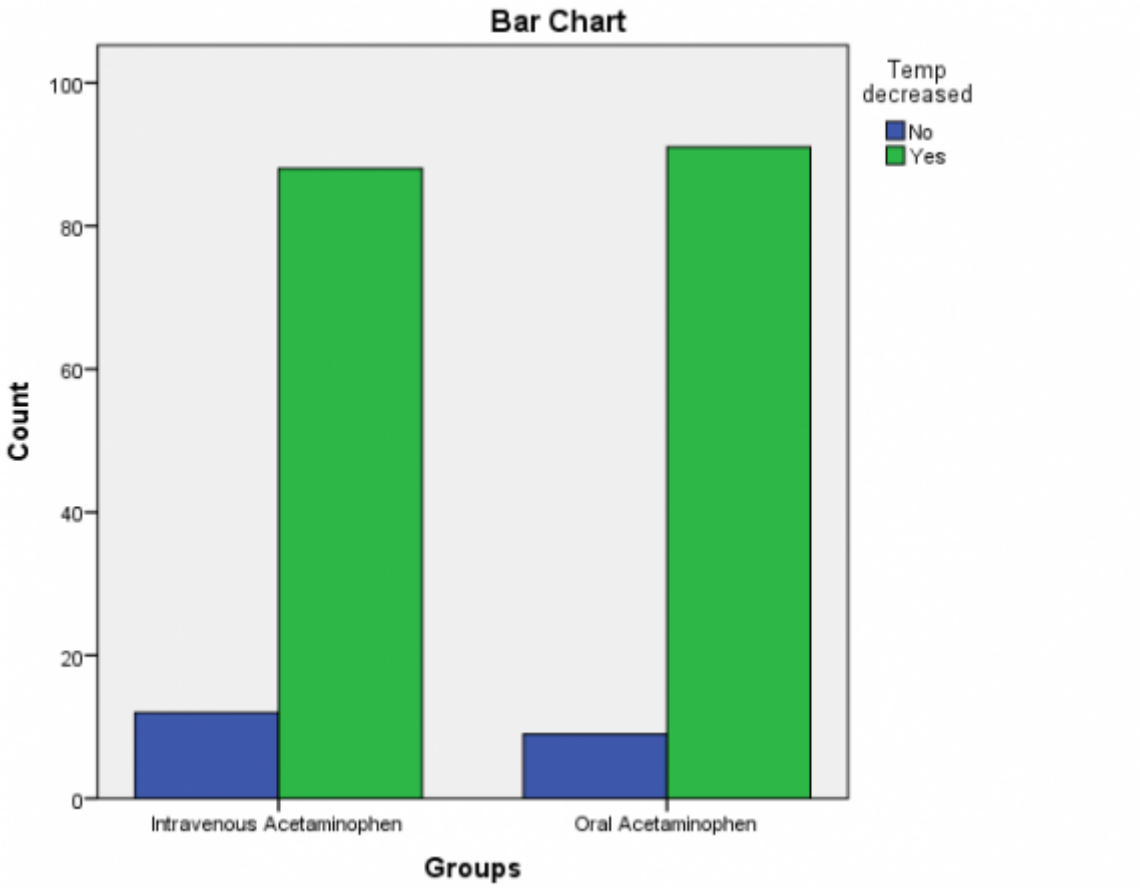


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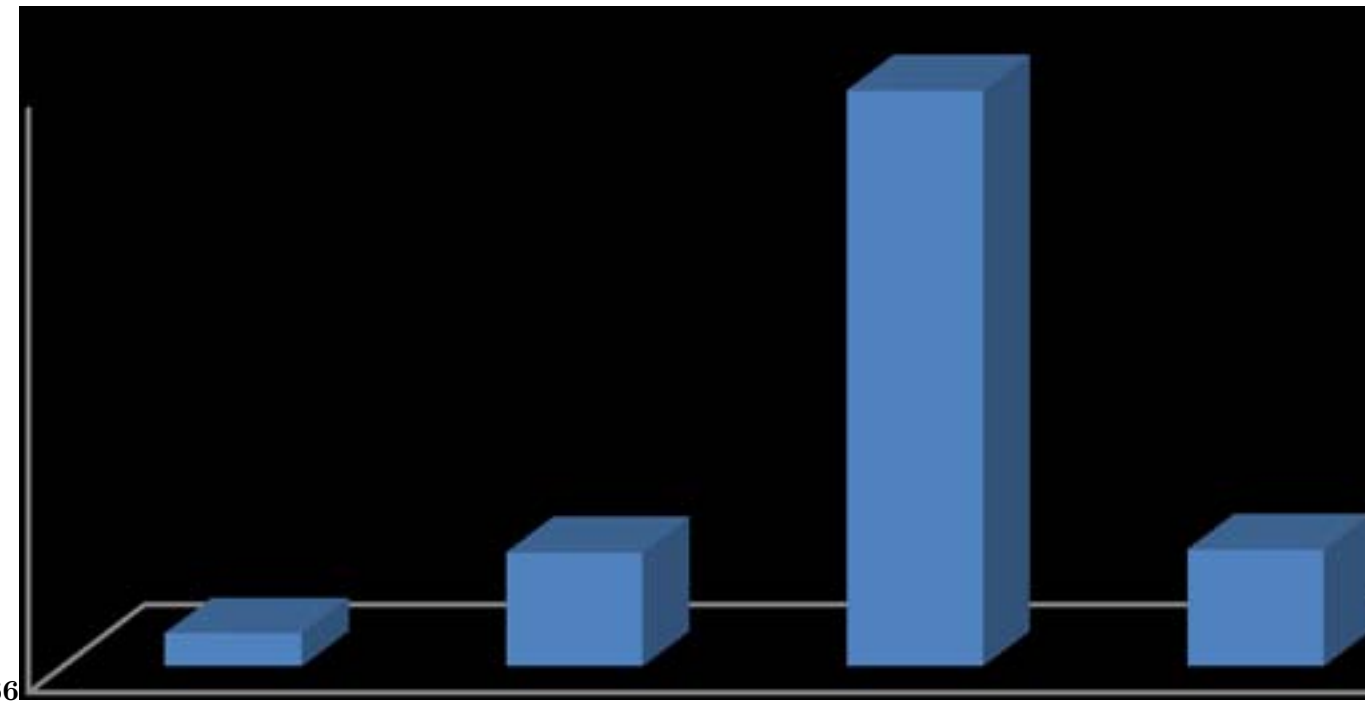
Figure 4: FFigure 4 :



**566**

Figure 5: Figure 5 :FTable 6 :Figure 6 :

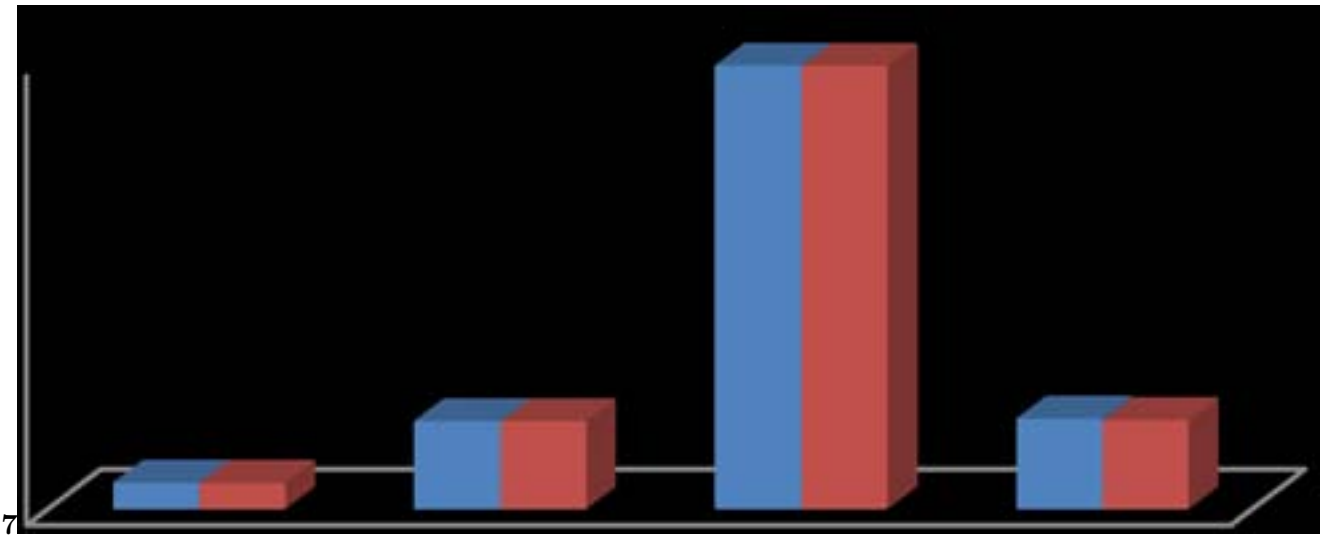


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Figure 6: Figure 7 :

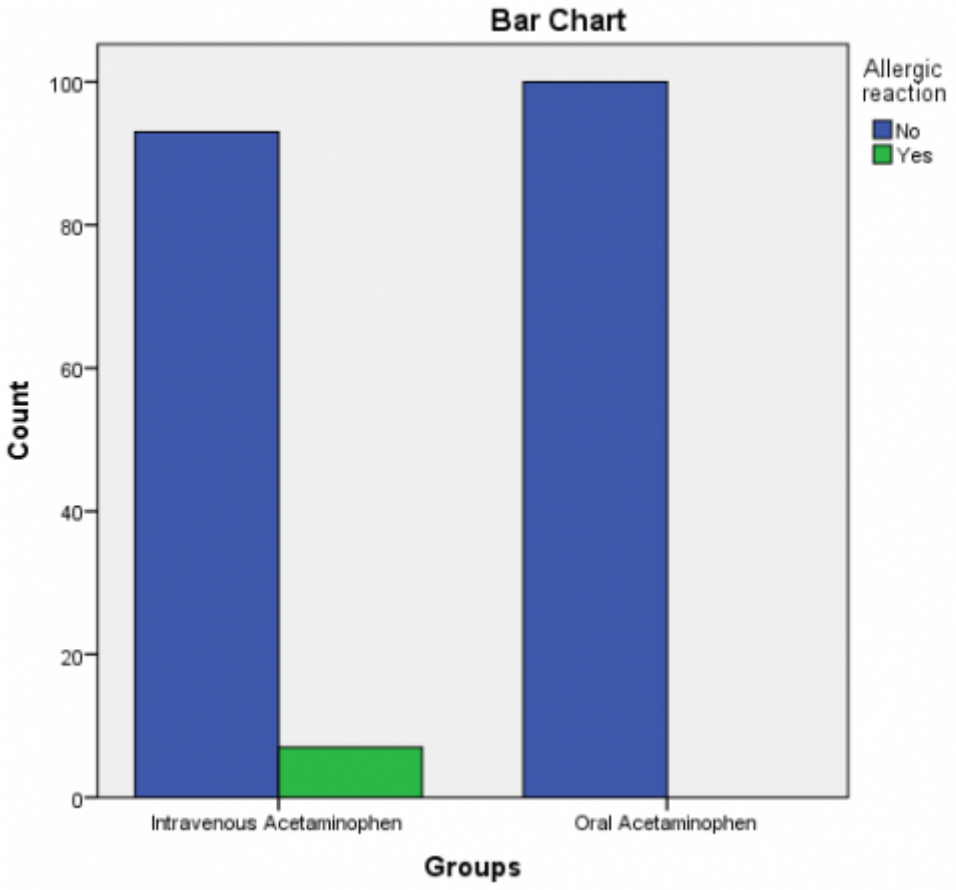


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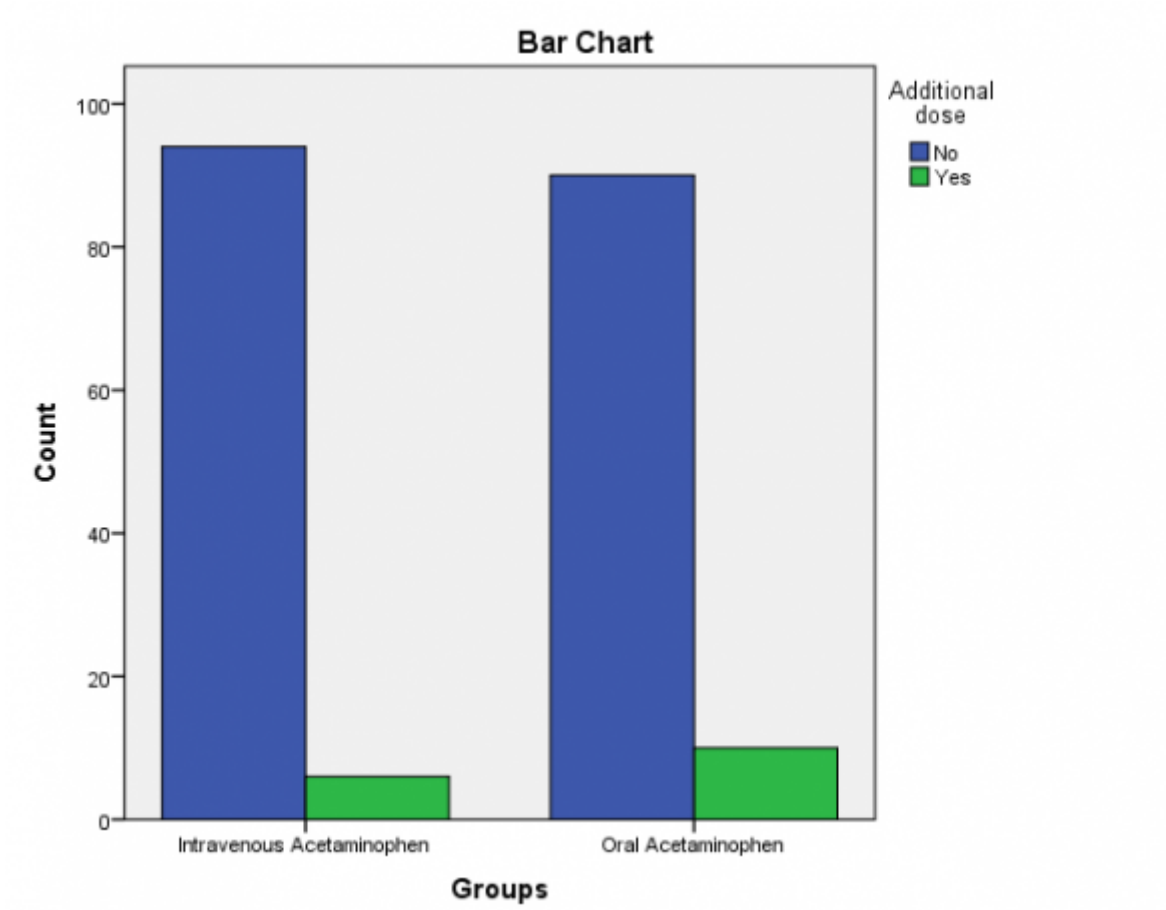
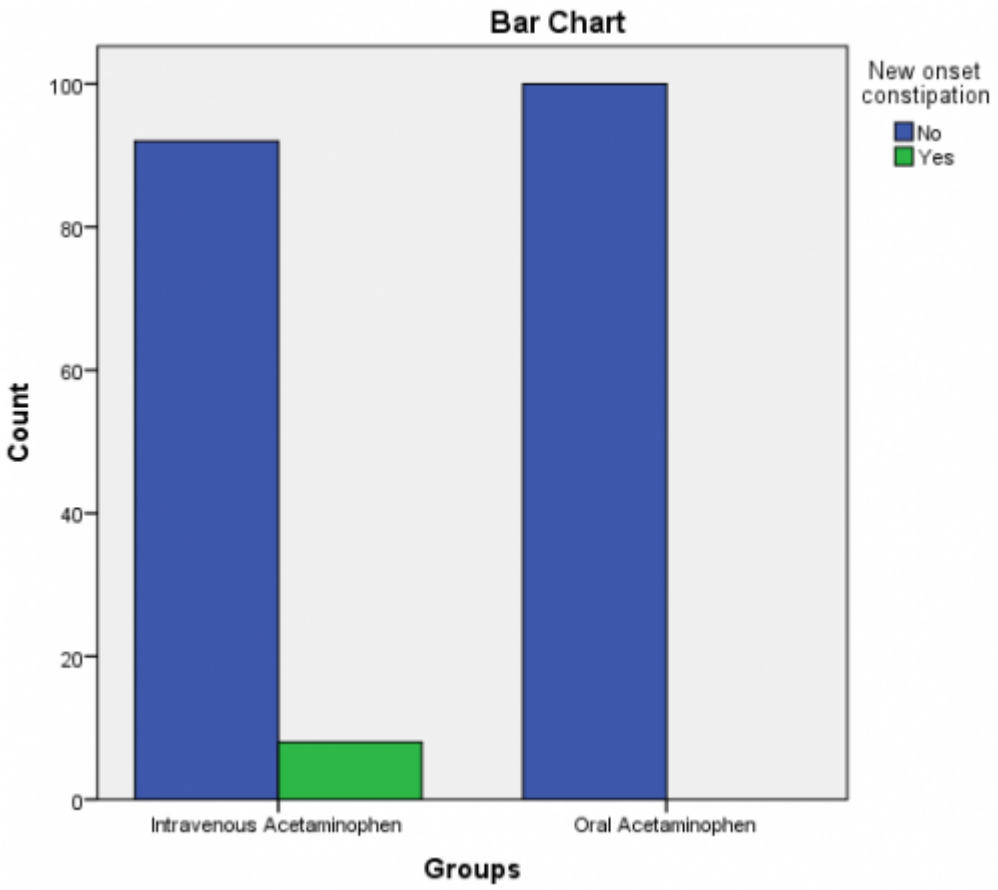
Figure 7: Figure 8 :



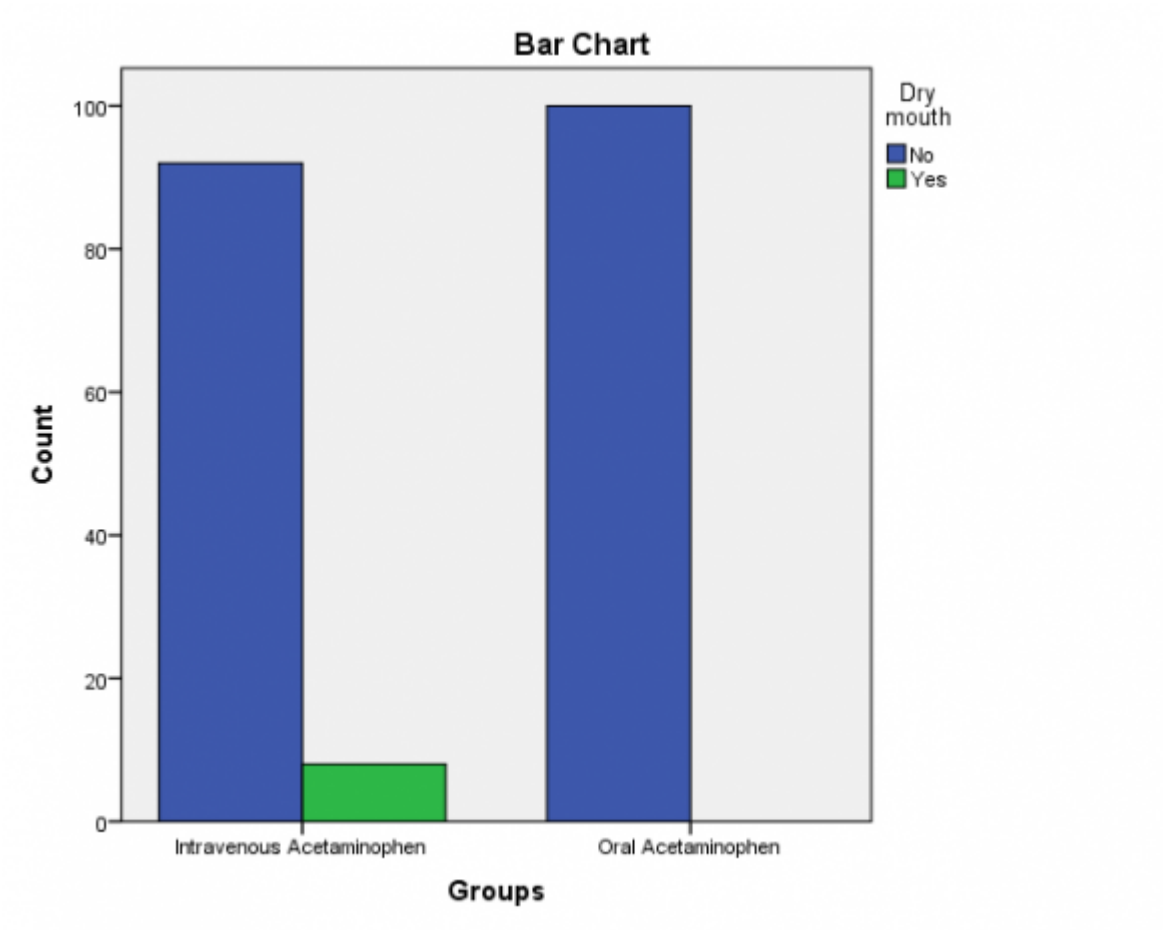

**9**

Figure 8: Figure 9 :




**10**

Figure 9: FFigure 10 :




**11**

Figure 10: FFigure 11 :

**2**

| Groups | Frequency | Percent |
|---|---|---|
| Intravenous Acetaminophen | 100 | 50.0 |
| Oral Acetaminophen | 100 | 50.0 |

*[Note: FTable 1: Study group DistributionFigure 1: Study group Distribution]*

Figure 11: Table 2 :

**3**

| | Crosstab | | | | |
|---|---|---|---|---|---|
| | | Male | Sex Female | Total | P-value |
| Groups Intravenous Acetaminophen | Number % of Total | 70 35.0% | 30 15.0% | 100 50.0% | 0.877 |
| Oral Acetaminophen | Number % of Total | 71 35.5% | 29 14.5% | 100 50.0% | |
| Total | Number % of Total | 141 70.5% | 59 29.5% | 200 100.0% | |

Figure 12: Table 3 :

**4**



| | | | | | | |
|---|---|---|---|---|---|---|
| Groups | Intravenous Acetaminophen | Crosstab Number | Temp decreased No | Yes | Total 100 | P-value 0.489 |
| | | % of Total | 44.0% | 4.5% | 50.0% | |
| | Oral Acetaminophen | Total Number | 21 | 179 | 200 | |
| | | % of Total | 10.5% | 89.5% | 100.0% | |
| | | Number | 9 | 91 | 50.0% | |
| | | Total | | | 100 | |

*[Note: © 2019 Global Journals]*

Figure 13: Table 4 :

**5**

| | | | | | |
|---|---|---|---|---|---|
| Mean | | 6.7742 | 23.2975 | 118.4400 | 23.9200 |
| Std. Error of Mean | | .19361 | .45287 | .65604 | .19637 |
| Median | | 6.2500 | 22.0000 | 122.0000 | 24.0000 |
| Mode | | 5.00 | 20.00 | 124.00 | 24.00 |
| Std. Deviation | | 2.73807 | 6.40452 | 9.27776 | 2.77708 |
| Percentiles | 25 | 5.0000 | 18.0000 | 112.0000 | 22.0000 |
| | 50 | 6.2500 | 22.0000 | 122.0000 | 24.0000 |
| | 75 | 9.0000 | 28.0000 | 126.0000 | 26.0000 |

*[Note: Base line Statistics of all CasesAge (in Yrs.)Weight (in Kgs) HR (per Min) RR (per Min)]*

Figure 14: Table 5 :

**7**

| | Group Statistics | | | | | |
|---|---|---|---|---|---|---|
| | Groups | N | Mean | Std. Deviation | Std. Error Mean | P-value |
| Age (in yrs.) | Intravenous Acetaminophen | 100 | 6.8085 | 2.65990 2.82707 | .26599 | .860 |
| | Oral Acetaminophen | 100 | 6.74 | | .28271 | |
| Weight (in Kgs) | Intravenous Acetaminophen | 100 | 23.295 | 5.98951 6.82464 | .59895 | .996 |
| | Oral Acetaminophen | 100 | 23.30 | | .68246 | |
| HR (per min) | Intravenous Acetaminophen | 100 | 118.44 | 9.3012 9.01949 | .93012 | .850 |
| | Oral Acetaminophen | 100 | 118.32 | | .90195 | |
| RR (per min) | Intravenous Acetaminophen | 100 | 23.92 | 2.41410 2.47460 | .24141 | .419 |
| | Oral Acetaminophen | 100 | 23.52 | | .24746 | |

Figure 15: Table 7 :

**8**

| | | Crosstab | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | Allergic reaction No | | Yes | | Total | | P-value |
| Groups | Intravenous Acetaminophen | Number % of Total | 93 | 46.5% | 7 | 3.5% | 100 | 50.0% | 0.007 |
| | Oral Acetaminophen | Number % of Total | 100 | 50.0% | 0 | 0.0% | 100 | 50.0% | |
| | Total | Number % of Total | 193 | 96.5% | 7 | 3.5% | 200 | 100.0% | |

Figure 16: Table 8 :

**9**

| | | Crosstab | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | Additional dose No | | Yes | | Total | | P-value |
| Groups | Intravenous Acetaminophen | Number % of Total | 90 | 45.0% | 6 | 3.0% | 100 | 50.0% | 0.297 |
| | Oral Acetaminophen | Number % of Total | 94 | 47.0% | 10 | 5.0% | 100 | 50.0% | |
| | Total | Number % of Total | 184 | 92.0% | 16 | 8.0% | 200 | 100.0% | |

Figure 17: Table 9 :

**10**

| | | Crosstab | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | New onset constipation No | | Yes | | Total | | P-value |
| Groups | Intravenous Acetaminophen | Number % of Total | 92 | 46.0% | 8 | 4.0% | 100 | 50.0% | 0.004 |
| | Oral Acetaminophen | Number % of Total | 100 | 50.0% | 0 | 0.0% | 100 | 50.0% | |
| | Total | Number % of Total | 192 | 96.0% | 8 | 4.0% | 200 | 100.0% | |

Figure 18: Table 10 :

**11**



| Groups | | | | | |
|---|---|---|---|---|---|
| | Intravenous Acetaminophen | Crosstab Number % of Total % | Dry mouth 46.0% | Total 100 | P-value |
| | | | No 92 4.0% | 50.0% | |
| | | | Yes 8 | 50.0% | 0.004 |
| | | of Total Number | 50.0% 0.0% | 200 | |
| | Total | % of Total Number | 192 8 | 100.0% | |
| | Oral Acetaminophen | | 96.0% 4.0% | 100 | |
| | | | 100 0 | | |

Figure 19: Table 11 :