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Comparative evaluation of the efficacy of intravenous paracetamol and ibuprofen on the treatment of tonsillopharyngitis with fever: A prospective, randomized controlled, double-blind clinical trial

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Abstract:

OBJECTIVE: Tonsillopharyngitis is one of the constituents of upper respiratory tract infection (URTI). Fever is a URTI symptom requiring treatment due to the occurrence of discomfort and high fever-based complications. This study primarily sets out to observe and compare the efficacy of intravenous administration of paracetamol and ibuprofen drugs on fever in adult patients with tonsillopharyngitis.

METHODS: This study was performed in a prospective, randomized controlled, double-blind design. The study population was divided as Group 1 (treated with paracetamol) and as Group 2 (treated with ibuprofen). While the first group was treated with paracetamol as 1000 mg in 150 ml normal saline, the second group was treated with ibuprofen as 400 mg in 150 ml normal saline. The primary outcome was the decrease in fever at 15, 30, and 60 min, while the secondary outcome was the need for additional treatment after 60 min.

RESULTS: One hundred and eighty-five patients were included in the final analysis. The mean age of the paracetamol group (57.4% male) was 28.36 ± 9.6, whereas that of the ibuprofen group (54.9% male) was 27.45 ± 7.98. Fever was reduced significantly between 0 and 60 min in both groups ($P \leq 0.001$ and $P \leq 0.001$, respectively). Although the antipyretic effect of ibuprofen was more pronounced in the early period than that of paracetamol, no significant difference was noted between the two groups in terms of fever drop between 0 and 60 min ($P = 0.350$).

CONCLUSION: Although both drugs prove effective in controlling fever at the 60 min, stronger efficacy of ibuprofen in the first 15 min may enable rapid discharge from the emergency department.

Keywords:

Emergency department, fever, ibuprofen, intravenous, paracetamol, upper respiratory tract infections

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Introduction

Mouth, nose, throat, larynx and trachea constitute upper respiratory tract, and among upper respiratory tract infections (URTI) are nasopharyngitis, acute sinusitis, tonsillitis, pharyngitis, laryngitis, and laryngotracheitis.[1] Although

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Box-ED Section:

What is already known on the study topic?

- Many patients presenting to emergency department (ED) with upper respiratory tract infection complaints often do so for the treatment of fever. Fast and effective treatment will both facilitate the working order of ED and improve patient comfort.

What does this study tell us?

- The data obtained from our study suggests that fever of the patients treated with ibuprofen decreases faster at the 15 min, though both drugs produce similar effects on fever at the 60 min. Therefore, the treatment of IV ibuprofen can be considered as the first-line choice in ED.

patients with URTI often present to outpatient clinics for ambulatory care, their admittance to emergency department (ED) are also common. Based on the data in the USA between 2014 and 2017, around 30% of emergency visits over the age of 18 are made by URTI patients.[2] Likewise, Ozdemir *et al*. reported that URTI patients constitute about 27% emergency visits in Turkey.[3] Although URTI can be accompanied by a range of symptoms such as fever, weakness, myalgia, pain, and cough, one of its most serious clinical signs is fever. Fever, which is defined as the measurement of body temperature above 38°C by tympanic measurement, is an acute adaptive physiological response to the infection-induced condition.[4] Even though mild fever (38.5°C–39°C) is part of the immune system's response, it may require treatment both due to patient discomfort and high fever-based complications (39°C–40°C). Therefore, mild fever can be reduced by drugs with antipyretic properties and by application of cold compress. It should also be noted that the principal aim of emergency antipyretic treatment is to bring fever back to its normal parameters immediately and avoid its recurrence after discharge.

First approved by FDA in 1951, paracetamol has been in use as an analgesic-antipyretic in the USA since 1955.[5] Paracetamol performs its antipyretic effect by blocking the production of prostaglandins with cyclooxygenase enzyme blockade in the production step of prostaglandins derived from arachidonic acid. With a similar effect to dose selective COX-2 inhibitors, the effect initiating time of paracetamol solution for infusion is 30 min after its administration, extending its antipyretic effect for no <6 h.[6,7]

On the other hand, ibuprofen, whose patent was granted in 1961, was introduced into the market to treat rheumatoid arthritis in the UK and in the USA in 1969 and 1974, respectively.[8] Ibuprofen, the first drug of propionic acid origin, creates its antipyretic effect by reversibly blocking cox enzymes.[9] Despite the recommendation of its infusion for 30 min, even its 5 or 7-min infusions are reported to achieve quick recuperation in a shorter infusion time.[10]

This double-blind study primarily sets out to observe and compare the efficacy of intravenous (IV) administration of long-used paracetamol and recently-used ibuprofen drugs on reducing fever in adult patients with tonsillopharyngitis, one of the constituents of URTI.

Methods

Study type

The approval to our study was granted by Pamukkale University Ethical Committee for Clinical Investigations with the decision number 60116787-020/75662 (dated October 30, 2018 and numbered 2018/20). This prospective, randomized controlled, double-blind clinical study was performed in the ED of Pamukkale University, Denizli, Turkey between November 30, 2018, and September 30, 2019. The approval of this equivalence study was given by the American clinical trial registry (NCT03918135 at https://clinicaltrials.gov).

Study population

The present study consisted of patients between 18 and 65 years who presented to ED in Pamukkale University with the URTI symptoms and a tonsillopharyngitis assessment (TPA) score of 5 and above [Table 1].[11] These URTI symptoms encompassed fever and one of the five indicators, including nasal congestion-sneezing and runny nose, conjunctival hyperemia and tear, cough and sputum, headache and muscle pain, and sore throat. After giving their informed consent, these subjects were enrolled in the study based on the inclusion and exclusion criteria [Figure 1].

Study design

The study population was divided into two groups as Group 1, treated with paracetamol and as Group 2, treated with ibuprofen. While the first group was provided with paracetamol (Parol 1000 mg, Mefar, Turkey) as 1000 mg in 150 ml normal saline, the second group was treated with ibuprofen (Intrafen 400 mg, Pharmavision, Turkey) as 400 mg in 150 ml normal saline.

The inclusion and exclusion criteria were specified prior to the study. The patients between 18 and 65 years, who had a body temperature more than 38°C, had a TPA score of 5 and above, had not been on any antipyretic drug in the last 4 h, had no history of antibiotic use for the past week, and agreed to take part in the study, were included within the framework of this study [Table 1].[11]

Table 1: Tonsillopharyngitis assessment score

Findings	0 point	1 point	2 points	3 points
Size of tonsils	Normal/absent	Slightly enlarged	Moderately enlarged	Much enlarged
Oropharynx color	Normal/pink	Slightly red	Red	Beefy red
Oral temperature (°C)	≤37	37.0-37.2	37-37.7	≥37.7
Number of oropharyngeal enanthems	None	Few	Several	Many
Size of the largest anterior cervical lymph nodes	Normal	Slightly enlarged	Moderately enlarged	Much enlarged
Number of anterior cervical lymph nodes	Normal	Slightly increased	Moderately increased	Greatly increased
Maximum tenderness of some anterior cervical lymph nodes	Not tender	Slightly tender	Moderately tender	Very tender

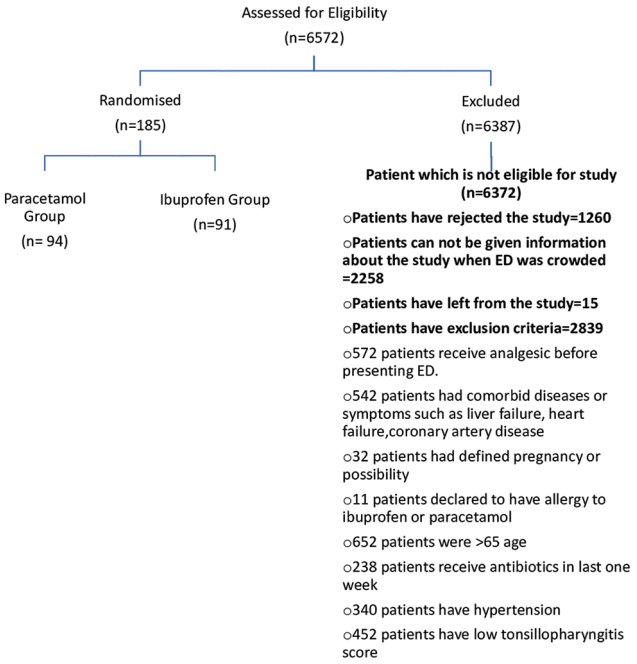

Figure 1: Flow chart

On the other hand, the exclusion criteria identified before the start of the study can be listed as follows: Being under 18 or over 65 years of age, refusing to participate, being uninformed about the study due to congestion in ED, using any antipyretic drug before 4 h of admittance to ED, being exposed to comorbid diseases (coronary artery disease, hypertension, and diabetes mellitus), being allergic to antipyretic drugs, having defined or possible pregnancy and breast-feeding, renal or liver transplantation, and being subjected to gastrointestinal bleeding and perforation due to previous intake of paracetamol and ibuprofen. Meanwhile, we did not exclude any patient from the study after determining the inclusion criteria.

The first examinations of the patients were carried out immediately on their admittance to ED. Tympanic body temperature is known to be the ideal method for measuring fever, and its measurement accuracy is more favorable due to its anatomical proximity to the thermoregulatory region. Thus, the examining physician measured and recorded the tympanic body temperatures of the patients during the examination with a tympanic infrared thermometer (nimomed® FT-F11, Fudakang Industrial Co. Ltd., Dong Guan City-PRC).

Randomization

This study followed a noncomplex randomization procedure. First, a randomization schedule was designed on SPSS software program by a statistics expert who was blinded to the study. Later, once a blinded physician obtained the informed consent forms, he assigned a number for each eligible patient in a sealed envelope. The study numbers as well as the information on which patients were paired with which drugs were known only to this blinded physician until the study was over.

The already-assigned study numbers were kept in opaque envelopes. After opening these envelopes in order, one of the ED nurses, also referred here as the study nurse, prepared the drug written in the envelope as described above. Then, the eligible patients were taken to the monitored surveillance unit, and while they were being monitored there, their IV access was established. The study drugs were administered to these patients by the other nurse who was uninformed about which drug to be given. These calibrated drugs were transparent and the same in appearance.

Following the randomization procedures, the target drugs were diluted in 150 ml of saline and given as IV fast infusion. As soon as IV treatment was administered, the examining physician, also blinded to the study drugs, measured and recorded the patients' body temperatures at the 0, 15, 30, and 60 min. In the meantime, their vital signs were checked against side effects during their observation.

Outcomes

The primary outcome of our study was the decrease in fever, while the secondary outcome was the need for additional treatment after 60 min. The degree of fever was checked by the thermometer. The fever reduction observed in patients was recorded at 15, 30, and 60 min after IV administration. The patients with fever of 38°C and above at the 60 min were administered with 500 cc normal saline or 500cc normal saline + cold compress as an additional therapy. The patients were not treated with other fever medications, except for the above-stated

drugs prepared in line with the "Good Manufacturing Practices" guidelines. Appropriate medical treatment was arranged at discharge for all the patients who discontinued or continued the study.

Sample size calculation and data analysis

The analysis of all the recorded data was performed in Statistical Package for Social Sciences 23.0 (IBM Corp., SPSS Inc., Chicago IL, USA) software program. A sample size calculation was conducted before the study to achieve a large effect size. Based on this calculation, 95% power within 95% confidence level could only be achieved if at least 144 patients (72 patients per group) took part in the study. To this end, 94 participants were recruited for the paracetamol group and 91 for the ibuprofen group in our study. As far as, the changing amount of fever is concerned, 97% power with 95% confidence was reached for the two medications (paracetamol dz: 2.71, ibuprofen dz: 3.22). Descriptive statistics were provided as median (interquartile range [IQR] 25–75) according to the distributions, while the mean scores were presented as mean ± standard deviation. A Kolmogorov–Smirnov test was performed to determine the level of normality, and the cut-off level for significance was set as $P < 0.05$ for all the analyses. A Chi-square analysis was performed for independent groups, whereas an Independent Samples *t*-test and Mann–Whitney *U*-test were run for normal and nonnormal distribution, respectively. On the other hand, a Friedman Test compared both groups for statistically repetitive measurements (fever).

Results

In our study, the paracetamol group was made up of 54 (57.4%) males, whereas the ibuprofen group was made up of 50 (54.9%) males. The mean age of the paracetamol group was 28.36 ± 9.6, and that of the ibuprofen group was 27.45 ± 7.98. The mean TPA of the paracetamol and ibuprofen groups turned out to be 10.28 ± 3.25 and 10.55 ± 3.4, respectively. No significant difference was noted between both groups with respect to gender, age, and TPA ($P = 0.732$; $P = 0.489$ and $P = 0.737$ respectively) [Table 2].

White blood cell count, neutrophil count, lymphocyte count, neutrophil percentage and lymphocyte percentage, and neutrophil/lymphocyte ratio as well as serum C-reactive protein were similar in both the groups ($P = 0.165$; $P = 0.235$; $P = 0.684$; $P = 0.508$; $P = 0.317$; $P = 0.347$; $P = 0.548$, respectively) [Table 2].

Fever median (IQR 25–75) value at baseline, 15, 30, and 60 min was calculated as 38.87 (38.4–39.3), 38.3 (37.8–38.9), 37.8 (37.2–38.5), and 37.2 (36.8–37.9) in paracetamol group, while 38.7 (38.2–29.1), 37.9 (37.5–38.4), 37.6 (37.1–38), and 37 (36.7–37.4) in ibuprofen group, respectively. Fever was reduced significantly between the baseline and 60 min in both groups ($P < 0.001$ and $P < 0.001$, respectively) [Figure 2]. Fever drop in the ibuprofen group significantly outpaced that of the paracetamol group between the baseline-15 min ($P = 0.036$). Although the antipyretic effect of ibuprofen proved stronger in the early period than that of paracetamol, no significant difference was observed between both groups in terms of fever drop between the baseline and 60 min ($P = 0.350$) [Table 3].

Twenty-two patients (23.4%) in the paracetamol group and 11 patients (12.1%) in the ibuprofen group had a fever of 38°C and above at the 60 min. A significant difference was evident between the two groups in relation to the requirement for additional treatment ($P = 0.044$). Accordingly, the paracetamol group outnumbered the ibuprofen group in terms of patients in need of additional therapy. The patients in both groups reported no side effects induced by paracetamol and ibuprofen intake.

Discussion

As far as the relevant literature is concerned, physicians tend to frequently resort to paracetamol and ibuprofen for fever and pain control. These two medication groups, notably their oral forms, are also largely

Table 2: Sociodemographic, clinical score, and laboratory parameter data of the groups

Variables	Paracetamol (*n*=94)	Ibuprofen (*n*=91)	*P*
Gender, *n* (%)			
Male	54 (57.4)	50 (54.9)	0.732*
Female	40 (42.6)	41 (45.1)	
Age, mean±SD	28.36±9.6	27.45±7.98	0.489†
TPA score, mean±SD	10.28±3.25	10.55±3.4	0.737‡
CRP, mean±SD	4.11±5.07	3.70±4.03	0.548†
WBC, mean±SD	10.99±4.24	11.56±3.94	0.165‡
Neutrophil count, mean±SD	8.70±3.97	9.07±3.63	0.235‡
Lymphocyte count, mean±SD	1.53±1.36	1.6±0.7	0.684†
Neutrophil (%), mean±SD	77.78±8.84	76.93±8.51	0.508†
Lymphocyte (%), mean±SD	13.82±6.99	14.87±7.25	0.317†
Neutrophil/lymphocyte ratio, mean±SD	7.44±5.19	6.79±4.04	0.347†
Fever levels at baseline, mean±SD	38.87±0.56	38.71±0.53	0.053‡

**P* value is derived from Chi-square test, †*P* value is derived from independent samples *t*-test, ‡*P* value is derived from Mann–Whitney U-test. SD: Standard deviation, TPA: Tonsillopharyngitis assessment, CRP: C-reactive protein, WBC: White blood cell

Table 3: Changes of the fever by the time in groups

Time	Median (IQR 25-75)		*P*
	Paracetamol	Ibuprofen	
Reduction 0-15th min	0.40 (0.10-1)	0.6 (0.3-1)	0.036*
Reduction 0-30th min	1.05 (0.4-1.43)	1.1 (0.6-1.5)	0.312*
Reduction 0-60th min	1.5 (0.98-2)	1.5 (1.2-1.9)	0.350*

**P* values are derived from Mann–Whitney U-test. IQR: Interquartile range

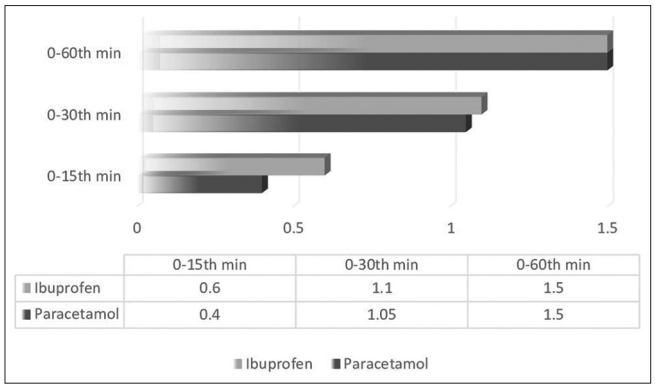

Figure 2: Reduction in fever in groups

preferred in the palliative treatment of fever induced by tonsillopharyngitis, which is highly common in the community. Indeed, a large body of research have so far investigated the pediatric effectiveness of oral forms on fever.[12] Besides, some previous research has made comparative evaluation of these two drugs, especially in the treatment of pain.[13,14] In this regard, our study is a first in the literature comparing the effectiveness of IV paracetamol and ibuprofen on fever management in adult patients in ED. It should also be noted that the two patient groups in our study did not differ in sociodemographic data and clinical scores as well as in laboratory parameters. Our study demonstrates that, although paracetamol and ibuprofen are potent drugs in the management of fever, ibuprofen seems more effective in the first 15 min.

Choi *et al*. concluded that IV propacetamol can act as a safe and effective agent for pediatric URTI patients who present with fever complaints, are unable to take oral medication, or are need of quicker fever control.[15] A clinical trial with 400 pediatric patients treated with oral or IV acetaminophen showed that fever values were lower in the IV paracetamol group at the 4th h, with no difference in fever values at the 6th h.[16] Another study investigating the superiority of ibuprofen against placebo in patients with malaria-induced fever revealed that fever could be controlled through 400 mg IV ibuprofen.[17] Overall, these studies indicate that drugs in IV form act faster and exert more antipyretic effectiveness than oral administration because of rapid circulation in the ED. In our study, we thus preferred the IV path for rapid fever control and quick discharge from ED.

Kauffman *et al*. compared the efficacy of oral ibuprofen and paracetamol treatment in a small sample size, concluding that ibuprofen could be a safe antipyretic agent.[18] Wong *et al*. provided a comparative evaluation of the efficacy of oral doses of dipyrone, ibuprofen, and paracetamol in a much larger population (628 children), suggesting that dipyrone and ibuprofen proved more effective than paracetamol in reducing fever.[19] In a multi-center, randomized controlled study on 103 pediatric patients, IV ibuprofen, or acetaminophen (oral or rectal) was administered to reduce fever, and IV ibuprofen was observed to achieve better fever reduction than acetaminophen at the 2nd h.[20] A meta-analysis performed by Narayan *et al*. reviewed 3023 articles related to oral paracetamol and ibuprofen in pediatric fever management, and in 6 out of 8 studies meeting the criteria, ibuprofen proved somewhat, though not significantly, more effective than paracetamol in reducing fever in children.[21] When it comes to our study, fever decline between baseline and 60 min remained unchanged in both groups, and we concluded that ibuprofen and paracetamol could be antipyretic equals. From this perspective, the results obtained in our study seem to validate the data reported in Narayan *et al*.'s meta-analysis.

Infusion duration is recommended to exceed 30 min in the administration of ibuprofen as an antipyretic.[22] Gan *et al*. reported that they provided IV ibuprofen with rapid infusion (over 5–10 min), suggesting that this form of infusion is safe during anesthesia induction.[23] Likewise, Bergese *et al*. observed the rapid infusion of ibuprofen to be safe and well-tolerated in their multicenter, open-label, surveillance trial, while Pavliv *et al*. showed that administration of ibuprofen with 5–7 min of rapid infusion in healthy people is safe and well-tolerated.[24,25] On the other hand, we found that fever decline in the ibuprofen group was higher than the one in the paracetamol group between baseline and 15 min, and what is striking in this sense is that ours is the first study to provide data on this issue. Ibuprofen is generally recommended to be administered over 30 min but also suggested to be given within 5–7 min by some studies in the literature, yet this drug was shown to reduce fever earlier through rapid infusion, as in our study. Considering the serious congestion in ED, this rapid infusion of ibuprofen might be more appropriate for use in the ED to achieve faster and more effective fever reduction. Furthermore, no side effects were reported in both groups during the conduct of our study. Especially the fact that no side or undesirable effects occurred despite the administration of IV ibuprofen through rapid infusion can promote the idea that it is safe to provide ibuprofen with rapid infusion.

Limitations

A range of limitations might have influenced the results obtained. Considering that this was a single-center study with restricted patient population, different assessments could have been made if this study had been carried out in other settings with a larger population. Furthermore, since we did not administer different doses of ibuprofen, we could not reveal whether 800 mg IV ibuprofen was superior to 1000 mg paracetamol in reducing fever, and

whether there was superiority discrepancy between 400 mg and 800 mg ibuprofen in terms of antipyretic efficacy.

Conclusion

Fever decrease remained higher in the ibuprofen group between the baseline and 15 min, but the efficacy of 1000 mg IV paracetamol treatment in patients admitted to ED with URTI complaints turned out to be similar to that of 400 mg IV ibuprofen treatment in terms of reducing fever. Although both drugs prove effective in controlling the fever at the 60 min, stronger efficacy of ibuprofen in the first 15 min may enable rapid discharge from ED. The percentage of requirement for additional treatment is approximately twice as high in the paracetamol group as in the ibuprofen group.

Author contribution statement

1. Study concept and design: A.Y. and G.O
2. Acquisition of data: G.O
3. Analysis and interpretation of data: A.Y., G.O. and R.S
4. Drafting of the manuscript: A.Y., G.O. and R.S
5. Critical revision of the manuscript for important intellectual content: A.Y. and G.O
6. Statistical analysis: R.S. and Y.K.C
7. Administrative, technical and material support: I.T., M.S., M.O., and U.C
8. Study supervision: A.Y.

Ethical approval

The approval to our study was granted by PamukkaleUniversity Ethical Committee for Clinical Investigationswith the decision number 60116787020/75662(dated October 30, 2018 and numbered 2018/20).

Conflicts of interest

None Declared.

Consent to participate

Subjects were included in the study after giving their informed consent.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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