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Comparison of Ibuprofen and Paracetamol for Fever Management in Sepsis and Septic Shock: A Randomized Controlled Trial

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Abstract

Aim: The aim of this study was to compare the efficacy of ibuprofen and paracetamol in fever management in patients with sepsis and septic shock and to evaluate their effects on body temperature and treatment outcomes.

Materials and Methods: This randomized, parallel-controlled, double-blind study was conducted at Ankara Bilkent City Hospital. Patients aged 18 years and older diagnosed with sepsis or septic shock and presenting with a fever of ≥38.3 °C were randomly assigned to receive either intravenous ibuprofen (400 mg) or paracetamol (1 g). Body temperature was measured before treatment and at 30, 60, and 120 minutes after treatment. The primary outcomes were changes in body temperature and the proportion of patients achieving a body temperature <38.3 °C. Secondary outcomes included rates of adverse effects, complications, and comparisons of severity scores (qSOFA, NEWS2, MEWS).

Results: After excluding patients with incomplete data, a total of 113 patients (64.6% female) were analyzed. Both groups demonstrated a reduction in fever at 30, 60, and 120 minutes. No significant differences were observed between the groups in demographic characteristics, clinical parameters, or severity scores ($p>0.05$). The most common source of infection was pulmonary, followed by urinary system infections. No significant difference in the distribution of infection sources was identified between the groups ($p>0.05$).

Conclusion: Although a significant effect favoring ibuprofen was observed at 30 minutes, both ibuprofen and paracetamol effectively reduced fever in patients with sepsis and septic shock, with no significant difference in efficacy between the two drugs over time.

Keywords: Sepsis, septic shock, ibuprofen, paracetamol, fever management

Introduction

Sepsis is a common and potentially life-threatening inflammatory syndrome caused by an excessive and dysfunctional response of the body to an infection (1). Septic shock occurs as an advanced stage of sepsis and is characterised by organ dysfunction and hypotension due to severe circulatory dysfunction (2). This condition can progress rapidly and significantly increase the patient's risk of death (3). For these reasons, sepsis should be recognised quickly, and treatment initiated early. The scoring used in the diagnosis and treatment of sepsis has been updated in the current guidelines. The latest guidelines recommend that the qSOFA score should not be used alone to diagnose sepsis (4). A study by Mellhammar et al. (5) reported that NEWS2 is superior to qSOFA in detecting sepsis and organ dysfunction. NEWS2 uses measurements such as respiratory rate, oxygen saturation, need for supplemental oxygen therapy, heart rate, blood pressure, level of consciousness, confusion, and body temperature in the context of "airway, breathing, circulation, disturbances and

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stress." In contrast to the qSOFA, this is a general assessment system for all clinical scenarios (6). The mEWS is a useful score for the emergency department and can be calculated more easily than the Early Warning score. It is calculated using 5 vital signs. It performs similarly to the NEWS2 score in predicting 30-day mortality (7).

Fever, which is also included in this scoring system, is a common symptom of sepsis that is generally thought to improve survival (8). The American College of Critical Care Medicine and the Infectious Diseases Society of America define fever as 38.3 °C and above, but there are different recommendations for fever between 38 and 38.5 °C (9,10). Experimental data suggest that elevated body temperature can slow the growth of microorganisms and enhance the host's immune response. However, the high energy expenditure caused by fever in patients with sepsis may exacerbate the life-threatening condition (8). Controlling fever is important for maintaining the balance of body systems and can help prevent potential complications and improve the patient's overall well-being (3). A recent controlled trial in patients with septic shock suggests that external cooling to reduce fever may reduce the need for vasopressors and improve early survival. However, the efficacy of antipyretic drugs in reducing body temperature remains unclear (8). Therefore, pharmacologic treatment of fever should be carefully planned, taking into account the patient's clinical condition (3). In this context, ibuprofen and paracetamol occupy an important place among the pharmacological agents commonly used to reduce fever (10).

In our literature search, we found no studies comparing these two drugs in patients with fever due to sepsis and septic shock. Comparing the efficacy of these two agents could help identify best practices in patient care and optimise treatment strategies. The main objective of this study was to compare the efficacy of ibuprofen and acetaminophen in the treatment of fever in patients with sepsis and septic shock. This study, which is designed as a randomised, controlled, double-blind trial, will comprehensively evaluate the efficacy of both drugs in reducing fever in the acute phase, as well as the response rates to treatment.

Materials and Methods

Study Design

This randomised, parallel-controlled, double-blinded study was conducted at Ankara Bilkent Hospital, a tertiary training hospital for emergency medicine. Patients over the age of 18 who presented to the hospital's emergency department with sepsis and septic shock between October 31, 2023 and October 31, 2024, were screened for possible inclusion in the study. Ethical approval was granted by the Ethics Committee of Ankara Bilkent Hospital No. 2 (desicion number: E2-23-4894, date: 06.09.2023). The study was also registered as a clinical trial with registration number NCT06061575. Patients were included in the study if they were classified as having sepsis and septic shock according to the "surviving sepsis campaign: International guidelines for management of sepsis and septic shock" (4), had a fever of 38.3 °C or more, were older than 18 years, and consented to participate in the study. All patients and their relatives were informed in detail about the study. All patients or their relatives signed a consent form agreeing to participate in the study.

Exclusion Criteria

Patients with a body temperature below 38.3 °C, patients for whom no written or verbal consent could be obtained from themselves or their relatives, patients with previous adverse reactions to the active substance ibuprofen or paracetamol, patients with chronic kidney and liver disease, pregnant women and patients with suspected pregnancy, patients with neuropsychiatric disorders and patients with neuropsychiatric drug use.

Intervention

Patients were divided into two groups: the Ibuprofen group and the Paracetamol group by computer-assisted 1:1 randomization method. In the double-blind study, similar vials were stored by removing the labels and numbering them according to the randomisation sequence. For the patient who met the eligibility criteria, the vial corresponding to the number in the randomisation sequence was delivered by the pharmacist, who removed the top cap, to the nurse who would administer the drug.

Ibuprofen Group: Patients received intravenous ibuprofen 400 mg (DORİFEN 400 mg/4 mL I.V. solution for infusion, VEM İLAÇ San. ve Tic. A.Ş, Tekirdağ/Türkiye).

Paracetamol Group: Intravenous paracetamol 1 g (PAROL 10 mg/mL Vial Containing Solution for Infusion, ATABAY KİMYA SAN. ve TİC. A.S., İstanbul/Türkiye) was administered to the patients.

The patients' body temperature was measured before treatment (minute 0) and 30, 60 and 120 minutes after treatment. The nurse who took the patient's temperature, the researcher who completed the case report form, and the patient were blinded.

The antipyretic effect of treatment was calculated using the differences between post-treatment and pre-treatment (minute 0) fever measurements in each patient: Diff-fever = baseline fever (minute 0) - fever at 30, 60, or 120 minute. Different fever

values were recorded and analysed separately for both groups. Patients for whom the fever measurements at 30, 60 and 120 minute could not be performed, for whom other data were missing, or whose data could not be accessed in any way, were not included in the analysis (per-protocol analysis).

Patients' qSOFA, NEWS2, and MEWS scores were assessed and recorded. Patients' comorbidities (e.g. diabetes, hypertension) were also recorded. Supportive care was provided in accordance with standard protocols for the treatment of sepsis and septic shock.

Primary and Secondary Outcomes

The differences between the baseline temperature values of the patients in the Ibuprofen and Paracetamol groups before treatment and the temperature values measured at 30, 60, and 120 minutes after treatment were compared and recorded as the primary outcome.

Treatment success, as the other primary outcome, was defined as a decrease in temperature below 38.3 °C and recorded as a dichotomous outcome.

The frequency and type of drug-related adverse reactions and possible complications after treatment were recorded as secondary outcomes. Comparative analyses of parameters such as severity score systems and focus of infection were also performed between the two groups.

Statistical Analysis

Study data were recorded on prepared case report forms and transferred to IBM Statistics for MacOS, version 28.0 (Armonk, NY: IBM Corp) for blinded analysis.

Normality of continuous data was assessed using the Shapiro-Wilk test, Q-Q plots, and histograms. Normally distributed parameters were presented as mean, standard deviation, and 95% confidence interval, while non-normally distributed parameters were expressed as median and interquartile range. The medians of non-normally distributed parameters were analysed by Mann-Whitney U test in pairwise comparisons, while the means of normally distributed parameters were compared by Independent sample t-test, in pairwise comparisons. Ratios of categorical data were analysed between groups by Pearson chi-square, or Fisher's exact test. The significance level was set at $p<0.05$.

Sample Size

In the power analysis based on the study by Alaje et al. (11), it was calculated that at least 42 patients should be included in each group with 80% power and 5% Type I error. However, to account for the possible loss of data and to increase the power of the study, the study was planned to include 120 patients, 60 patients in each group.

Results

Demographic and Clinical Characteristics

Demographic and clinical characteristics of the patients in Ibuprofen and Paracetamol groups are presented in Table 1. It was planned to include a total of 120 patients in the two groups, but 2 patients in the Ibuprofen group and 5 patients in the Paracetamol group were lost to follow-up in terms of controlling body temperature and other parameters. As a result, the data of a total of 113 patients, 64.6% of whom were female, were analysed using the per-protocol analysis principle (Figure 1).

When the demographic and clinical characteristics of Ibuprofen and Paracetamol groups were compared, no statistically significant difference was found between the groups in parameters such as age, height, weight, systolic and diastolic blood pressure, pulse rate, and oxygen saturation ($p>0.05$). However, respiratory rate was significantly higher in the Paracetamol group ($p=0.003$).

There was no significant difference between the groups in terms of gender distribution, comorbidities such as diabetes mellitus, malignancy, chronic obstructive pulmonary disease, congestive heart failure, coronary artery disease, oxygen support, and hypercapnic respiratory failure ($p>0.05$). However, the frequency of hypertension was significantly higher in the Ibuprofen group than in the Paracetamol group ($p=0.022$).

No significant difference was observed between the qSOFA, NEWS2, and MEWS scores of the groups ($p>0.05$). In addition, no significant difference was found between the groups in terms of the frequency of confusion and other clinical conditions ($p>0.05$).

Foci of Infection

Table 2 shows the distribution of foci of infection in the Ibuprofen and Paracetamol groups. When analysing the distribution of infection sites in the Ibuprofen and Paracetamol groups, it was found that the most common infection site in both groups was the pulmonary site, with 50.0% in the Ibuprofen group and 41.8% in the Paracetamol group ($p=0.288$). The rate of urinary tract infections was higher in the Paracetamol group (27.3%) compared to the Control group (17.2%); however, this difference was not statistically significant ($p>0.05$).

Gastrointestinal tract infections were only observed in the Ibuprofen group (5.29%), while the distribution of soft tissue infections and other sources of infection showed no significant difference between the groups ($p>0.05$).

Table 1. Comparison of demographic and clinical characteristics between the Ibuprofen and Paracetamol groups				
Variables		**Ibuprofen**	**Paracetamol**	**p value/(Diff % -95% CI)**
Age		64.39±16.93	61.16±18.52	0.335/(-3.37-9.84)*
Gender	Male	22 (37.9)	18 (32.7)	0.563†
	Female	36 (62.1)	37 (67.3)	
Height (cm)		169.44±7.78	170.09±9.43	0.693 (-3.86-2.57)*
Weight (kg)		73.67±12.96	73.87±14.40	0.938 (-5.30-4.90)*
SBP		124.91±28.30	122.69±27.77	0.675/(-8.23-12.68)*
DBP		69.70±12.98	70.90±12.42	0.616/(-5.94-3.54)*
Pulse rate (/min)		96.50±16.70	101.01±18.16	0.171/(-11.01-1.98)*
Oxygen saturation (%)		94.00 (90.75-95.00)	93.00 (88.00-96.00)	0.364‡
Respiratory rate (/min)		18.00 (17.00-20.25)	21.00 (18.00-22.00)	0.003‡
COPD		9 (15.5)	5 (9.1)	0.300†
CAD		11 (19.0)	8 (14.5)	0.530†
CHF		5 (8.6)	3 (5.5)	0.717§
HT		28 (48.3)	15 (27.3)	0.022†
DM		14 (24.1)	15 (27.3)	0.703†
Malignancy		13 (22.4)	9 (16.4)	0.417†
Others		24 (41.4)	22 (40.0)	0.881†
Oxygen support		33 (56.9)	25 (45.5)	0.224†
Hypercapnic respiratory failure		16 (27.6)	12 (21.8)	O.478†
Confusion		28 (48.3)	22 (40.0)	0.376†
qSOFA score		2.0 (2.0-2.0)	2.0 (2.0- 2.0)	0.606‡
NEWS2		9.0 (8.0-10.0)	9.0 (8.0-12.0)	0.444‡
MEWS		5.0 (4.0-6.0)	5.0 (4.0-6.0)	0.272‡

*Independent sample t test, Mean ± SD; †Pearson chi-square test, n (%); ‡Mann-Whitney U test, Median (25-75%); §Fisher's exact test, n (%).
SBP: Systolic blood pressure, DBP: Diastolic blood pressure, COPD: Chronic obstructive pulmonary disease, CAD: Coronary artery disease, CHF: Congestive heart failure, HT: Hypertension, DM: Diabetes mellitus, qSOFA: Quick sequential organ failure assessment, NEWS2: National early warning score 2, MEWS: Modified early warning score, CI: Confidence interval, Diff: Difference

Treatment Efficacy

Table 3 summarises the fever measurements of the patients in the Ibuprofen and Paracetamol groups at the beginning (0 minute), after 30, 60, and 120 minutes, as well as the changes in fever (diff-fever) over time. When comparing the fever measurements and the changes over time in the Ibuprofen and Paracetamol groups, no statistically significant difference was found between the measurements at the beginning (fever -0), at the 30th minute (fever -30), at the 60th minute (fever -60) and at the 120th minute (fever -120).

When the changes in fever were analyzed, it was found that the change in fever -30 was significantly greater in the Ibuprofen group than in the Paracetamol group (1.54±0.77 vs. 1.22±0.73, p=0.026). However, there was no significant difference (p>0.05) between the groups in the changes in fever -60 and fever -120. Fever values of 2 patients in the Ibuprofen group and 1 patient in the Paracetamol group, did not fall below 38.3 °C (p=0.496, Fisher's exact test).

These findings indicate that both treatments had a similar efficacy in terms of reducing fever; but the Ibuprofen group provided a more rapid decrease in fever at 30 minutes.

The left panel of Figure 2 shows the baseline (0 minute) temperature measurements and the mean temperature measurements at 30, 60, and 120 minute in the Ibuprofen and Paracetamol groups with 95% confidence intervals. In both groups, a steady decrease in temperature was observed over time. At 30 minutes, the Ibuprofen group showed a slightly faster decrease in temperature compared to the Paracetamol group, but this difference decreased at subsequent time points. The confidence intervals overlapped, showed similar efficacy.

The right panel shows the changes in fever (diff-fever) in both groups at 30, 60, and 120 minutes. The Ibuprofen group showed a significantly greater decrease in fever at 30 minutes compared to the Paracetamol group (p=0.026). However, when the changes at 60 and 120 minutes were compared between the groups, they were similar and the confidence intervals overlapped.

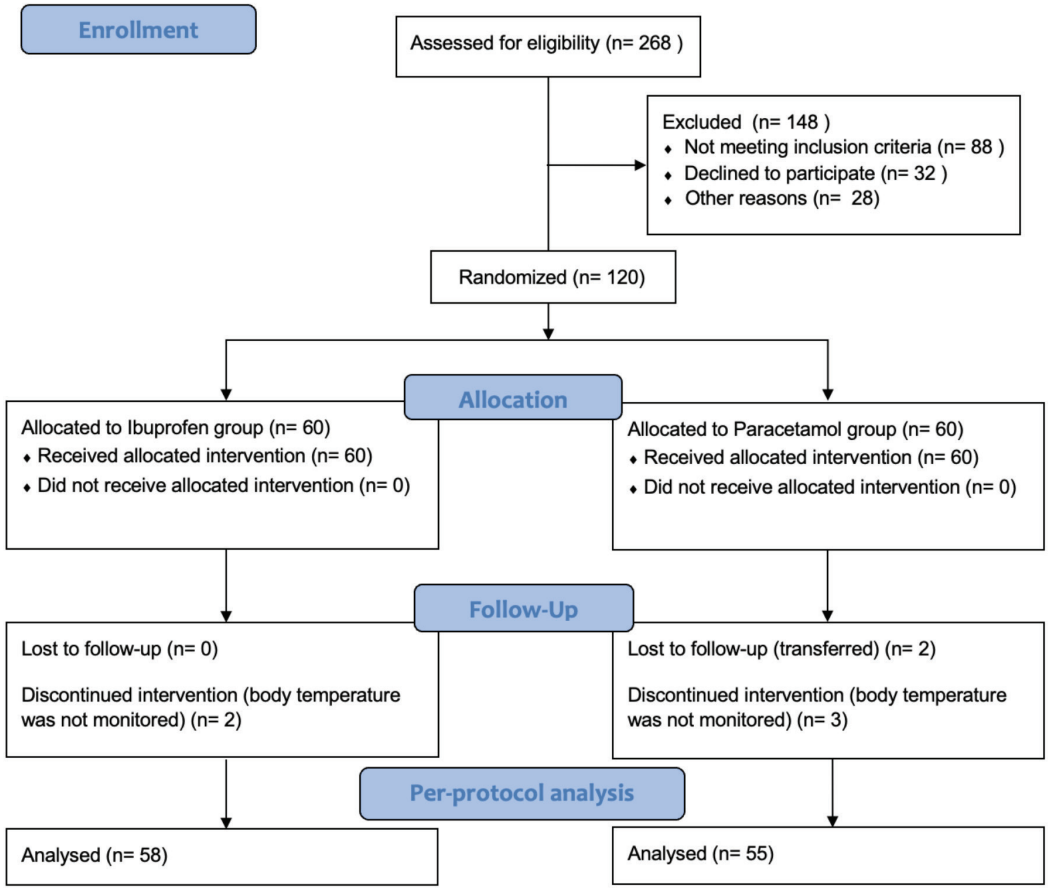

Figure 1. Flowchart of the study

Table 2. Distribution of infection foci between the Ibuprofen and Paracetamol groups

Variables	Ibuprofen	Paracetamol	Total	p value
Pulmonary	29 (50.0)	23 (41.8)	52 (46.0)	0.288
Urinary system	10 (17.2)	15 (27.3)	25 (22.1)	
Gastrointestinal system	3 (5.29	0 (0.0)	3 (2.7)	
Soft tissue	5 (8.6)	7 (12.7)	12 (10.6)	
Others	11 (19.0)	10 (18.2)	21 (18.6)	
Total	58 (100.0)	55 (100.0)	113 (100.0)	
Pearson chi-square test, n (%)				

Side Effects and Complications

No side effects or complications related to the drugs used in the study were observed, except for mild nausea in one patient in the Ibuprofen group.

Discussion

In this study, we aimed to compare the efficacy of ibuprofen and paracetamol in the management of fever in patients with sepsis and septic shock. Our results showed that both drugs were effective in reducing fever, but ibuprofen reduced fever more rapidly. This is the first randomised controlled double-blind study in the management of fever in patients with sepsis and septic shock.

Fever is a pathophysiological and clinically important symptom in patients with sepsis. Although fever is recognised as the body's attempt to fight infection, excessively elevated body temperature can lead to cellular damage, organ dysfunction and increased metabolic demands. Therefore, controlling fever may be a critical step in sepsis management (8). In our study, although both drugs were similarly effective in controlling fever, ibuprofen

Table 3. Comparison of fever measurements and changes over time between the Ibuprofen and Paracetamol groups			
Variables	**Ibuprofen**	**Paracetamol**	**p value/(Diff -95% CI)**
Fever -0	38.65±0.50	38.56±0.42	0.267/(-0.07-0.27)*
Fever -30	37.11±0.75	37.33±0.75	0.118/(-0.50-0.05)*
Fever -60	36.88±0.63	36.86±0.64	0.913/(-0.22-0.25)*
Fever -120	36.76±0.55	36.84±0.59	0.462/(-0.29-0.13)*
Diff-fever -30	1.54±0.77	1.22±0.73	0.026/(0.03-0.60)*
Diff-fever -60	1.78±0.73	1.69±0.75	0.524/(-0.18-0.36)*
Diff-fever -120	1.89±0.67	1.72±0.59	0.139/(-0.05-0.41)*
Persistent fever above 38.3 °C	2 (3.4)	1(0.0)	0.496†
*Independent sample t test, Mean ± SD; †Fisher's exact test, n (%), CI: Confidence interval, Diff: Difference			

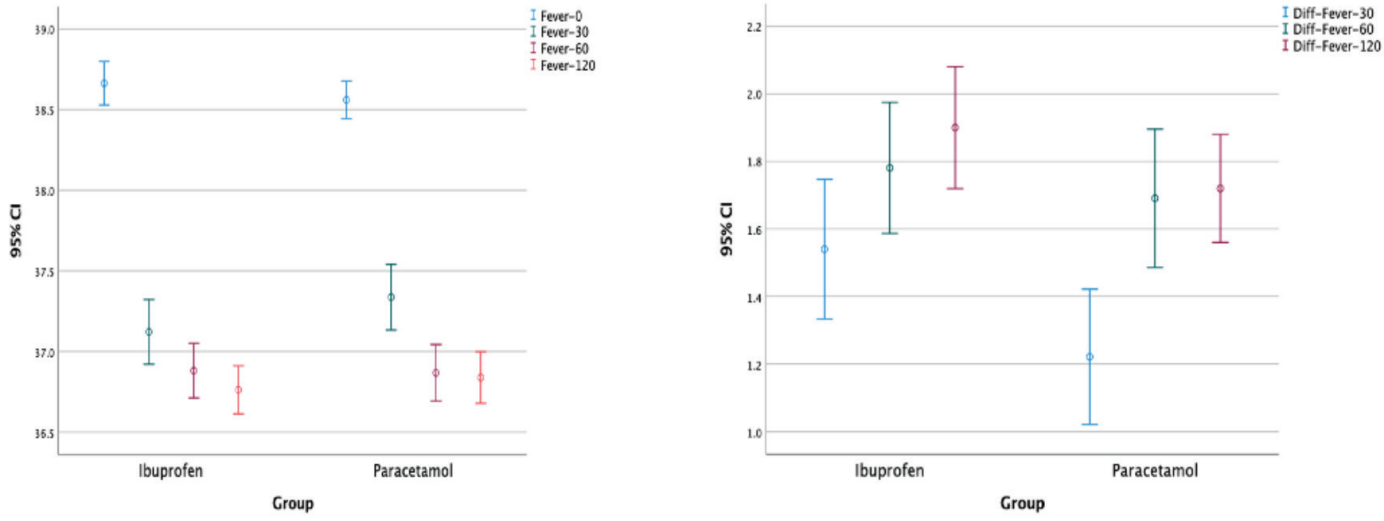

Figure 2. Comparison of fever measurements and changes over time between the Ibuprofen and Paracetamol groups

showed faster results. This difference may be due to the anti-inflammatory properties of ibuprofen, which suppress the body's inflammatory response and reduce fever faster.

In the literature, some randomised controlled trials on the management of fever, have reported similar efficacy of both drugs. For example, Can et al. (9) reported that both groups had similar efficacy when fever measurements at 15, 30, and 60 minutes were analyzed. In our study, although the difference in fever value at 30 minutes, in favour of ibuprofen, was significant, the efficacy of both groups was similar at 60 minutes. Although this is consistent with the literature, it is not possible to make a definite comment on this issue, since our data at 120 minutes needs to be compared.

In another study, Oncel et al. (12) compared ibuprofen and paracetamol in the treatment of fever secondary to tonsillopharyngitis, and reported that ibuprofen showed faster antipyretic activity at 15 minutes, but antipyretic activities were similar at 60 minutes. In our study, the antipyretic activity of the Ibuprofen group was more effective at 30 minutes, and there was no significant difference between the groups at 60 minutes. However, it was not possible to comment on the data at 120 minutes.

Kauffman et al. (13) compared the efficacy of oral ibuprofen and paracetamol in a small sample and stated that ibuprofen may be a safe antipyretic agent. In addition, Wong et al. (14) evaluated the efficacy of oral dipyrone, ibuprofen, and paracetamol doses and suggested that dipyrone and ibuprofen were more effective than paracetamol in reducing fever. In our study, compared to these two studies, although a difference was observed in favour of ibuprofen at 30 minutes, no statistical difference was found between the groups at 60 minutes. This result is not fully compatible with the literature. Jamerson and Haryadi (15) stated that the antipyretic effect of ibuprofen was stronger than that of paracetamol in COVID-19 patients. Especially in comparative studies conducted in children and adults, it was observed that ibuprofen reduced fever more effectively, and this effect lasted

longer. In another study conducted in healthy men aged 18-55 years, it was reported that the combination of ibuprofen 250 mg and paracetamol 500 mg had a more rapid onset of action within 6-8 hours compared to the treatment doses given alone, but all three groups showed similar antipyretic efficacy (16).

In a review of studies in the paediatric population aged 1 month to 12 years, it was reported that ibuprofen reduced fever slightly more effectively than paracetamol in six studies, but this difference was not statistically significant. However, it is generally concluded that both drugs are equally effective (17).

It was also shown that there was no significant difference between the two drugs at doses recommended by the doctor (paracetamol 15 mg/kg, ibuprofen 10 mg/kg) up to 6 hours, and in the 6-48 hour interval. However, in this review, it was reported that ibuprofen was more effective in some studies at over the counter doses (paracetamol 10-15 mg/kg, ibuprofen 2.5-10 mg/kg) (18). In another study conducted with a group of paediatric patients admitted to the emergency department due to fever, ibuprofen was reported to reduce fever more effectively than paracetamol (19). However, at this point, there are situations where the results of our study partially overlap with the literature.

In terms of side effect profile, the results of our study are largely compatible with previous studies in the literature. Derry et al. (20) reported that no serious side effects were observed in ibuprofen and paracetamol combinations. In a systematic review conducted by Alnasser et al. (21) for episodic tension type headaches, it was stated that ibuprofen is less likely to cause general and gastrointestinal side effects compared to placebo and paracetamol, but paracetamol may be preferred in high-risk individuals (e.g., those with renal failure or risk of gastrointestinal bleeding). Another study comparing ibuprofen and paracetamol in the treatment of fever due to tonsillopharyngitis reported that no side effects were observed in either group (12). The side effect profile of our study, generally, supports the literature.

When the literature is analysed, it is seen that ibuprofen is either more effective and faster or has efficacy similar to paracetamol, although there are different disease and age groups. However, ibuprofen shows a superior antipyretic effect in our study at 30 minute, but has similar efficacy at 60 and 120 minute. In light of these findings, we conclude that the pharmacological treatment approach in patients with sepsis should be carefully selected according to the patient's general condition, comorbidities, and response to treatment.

In our study, no significant difference was found in the response rates to treatment, suggesting that both drugs have similar effects in terms of controlling fever. This finding suggests that ibuprofen and paracetamol can be used as effective treatment options in patients with sepsis and septic shock.

Study Limitations

The study has several limitations. These include it was conducted as a single-centre study, the lack of fever monitoring after 120 hours, and the differences in parameters, such as respiratory rate and the presence of hypertension, which affect standardisation between the two groups.

The rapid effect of ibuprofen may be particularly important for symptomatic relief in patients who are unwell because of high fever. However, its effect on long-term patient outcomes should be evaluated in future studies. Although no serious adverse events were reported in the trial, the potential side effects of ibuprofen in long-term use, especially in patients with risk factors such as renal failure or a history of gastrointestinal ulcers, should be considered. Therefore, clinicians must carefully assess patient characteristics when prescribing ibuprofen.

In addition, given the pharmacokinetic properties of ibuprofen and paracetamol, the 120 minute follow-up period in our study may not be sufficient to evaluate long-term antipyretic efficacy. However, this duration is useful for assessing early response during the acute phase. Longer follow-up periods are recommended for future studies.

Conclusion

In conclusion, ibuprofen and paracetamol are effective in the management of acute fever in patients with sepsis and septic shock, and both drugs can be used safely in the treatment of patients. However, it is important to individualise treatment protocols by considering the advantages and disadvantages of both drugs. Factors such as general condition, age and comorbidities may affect the choice of medication and should be carefully evaluated during the treatment process.

Ethics

Ethics Committee Approval: Ethical approval was granted by the Ethics Committee of Ankara Bilkent Hospital No. 2 (desicion number: E2-23-4894, date: 06.09.2023).

Informed Consent: All patients or their relatives signed a consent form agreeing to participate in the study.

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Footnotes

Author Contributions

Surgical and Medical Practices: SD., AŞ., HO., Concept: SD., AŞ., HO, MY.,NİI., Design: SD., AŞ., HO, İA., Data Collection or Processing SD., AŞ., HO., Analysis or Interpretation: SD., AŞ., VS.,RİM., Literature Search: SD., AŞ.,İA., VS., RİM., MY., HO., Writing: SD., AŞ.,İA., NİI., VS., RİM., MY., HO.

Conflict of Interest: The authors declare that they have no conflict of interest.

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