Research note

Ibuprofen use and clinical outcomes in COVID-19 patients

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ABSTRACT

Objective: It was recently suggested that ibuprofen might increase the risk for severe and fatal coronavirus disease 2019 (COVID-19) and should therefore be avoided in this patient population. We aimed to evaluate whether ibuprofen use in individuals with COVID-19 was associated with more severe disease, compared with individuals using paracetamol or no antipyretics.
Methods: In a retrospective cohort study of patients with COVID-19 from Shamir Medical Centre, Israel, we monitored any use of ibuprofen from a week before diagnosis of COVID-19 throughout the disease. Primary outcomes were mortality and the need for respiratory support, including oxygen administration and mechanical ventilation.
Results: The study included 403 confirmed cases of COVID-19, with a median age of 45 years. Of the entire cohort, 44 patients (11%) needed respiratory support and 12 (3%) died. One hundred and seventy-nine (44%) patients had fever, with 32% using paracetamol and 22% using ibuprofen, for symptom-relief. In the ibuprofen group, 3 (3.4%) patients died, whereas in the non-ibuprofen group, 9 (2.8%) patients died (p 0.95). Nine (10.3%) patients from the ibuprofen group needed respiratory support, compared with 35 (11%) from the non-ibuprofen group (p 1). When compared with exclusive paracetamol users, no differences were observed in mortality rates or the need for respiratory support among patients using ibuprofen.
Conclusions: In this cohort of COVID-19 patients, ibuprofen use was not associated with worse clinical outcomes, compared with paracetamol or no antipyretic. **E. Rinott, Clin Microbiol Infect 2020;26:1259.e5—1259.e7**

Introduction

The current outbreak of coronavirus disease 2019 (COVID-19), caused by the novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has rapidly spread throughout the world, and has become a worldwide pandemic with more than two million confirmed cases by mid-April 2020. Though COVID-19 is primarily a respiratory disease, its insidious and non-specific clinical course can result in a delayed diagnosis and a prolonged period of self-administered symptomatic treatment. As fever is one of the most common symptoms of COVID-19, antipyretic medications, including ibuprofen, play an important role in controlling patients' symptoms.

On 14 March 2020, during the emergence of the COVID-19 outbreak, the French Minister of Health published a recommendation to avoid the use of anti-inflammatory medications like ibuprofen or cortisone, claiming it could aggravate infections [1]. Though no reference was provided, the statement may stem from a report published by the French Agency for the Safety of Health Products, concerning 400 cases of severe infections that were linked temporally to ibuprofen administration [2]. Adding to these concerns, recent *in vitro* work has supported the hypothesis that pathogenic coronaviruses have a high affinity to the angiotensin converting enzyme 2 (ACE2) receptor, and that ACE2 production as

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well as the ACE 2 receptor expression, can be increased by ibuprofen [3,4].

The public statement prompted a global debate about the safety of ibuprofen as an antipyretic treatment for individuals with confirmed or even suspected COVID-19 during the current pandemic [1,5]. Several national health agencies worldwide, including the WHO, have responded with official statements emphasizing that no evidence supports these claims [6—8]. Nevertheless some authorities, erring on the side of caution while awaiting clinical data, have suggested that paracetamol should be considered the recommended first-line antipyretic, with ibuprofen reserved for individuals who are unable to tolerate paracetamol [9].

In the current study, we aimed to evaluate whether ibuprofen administration to individuals with COVID-19 was associated with worse clinical outcomes, compared with paracetamol or no antipyretic.

Methods

We conducted a retrospective cohort study of SARS-CoV-2-positive patients tested at the Shamir Medical Centre, Israel, between 15 March and 15 April 2020. At that time the policy of the Israeli Ministry of Health was to test every patient with symptoms that could be compatible with COVID-19 (cough, dyspnoea, fever). Nasopharyngeal swabs were tested by real-time RT-PCR in the hospital's molecular laboratory that is approved by the Israeli Ministry of Health. Patients were contacted by phone (mean 13 days after the diagnosis, range 2—30 days), and a short structured questionnaire was administered. Information collected included age, gender, chronic diseases and medications, date of diagnosis, symptoms and factors relating to the clinical course of disease (admission to the hospital and the intensive care unit, need for oxygen or ventilation). For our purposes, severe disease was defined as needing any respiratory support (supplemental oxygen administration or ventilation), admission to intensive care unit or death. Patients were asked about the use of any medication containing ibuprofen (a complete list of local commercial names was supplied), paracetamol or dipyrone starting a week before diagnosis of COVID-19. In the case of mortality, information was obtained from medical charts and referral letters. Chi-square test of independence, Wilcoxon rank-sum test and Fischer's exact test were applied as needed (significance threshold, $p < 0.05$). Statistical analyses were performed using R software, version 3.5.3. The study was approved by the Shamir Medical Centre Institutional Review Board.

Results

The study population included 403 confirmed cases of COVID-19 of 437 positive patients during the inclusion period (92%). Median age was 45 years, 220 (55%) were male and 101 (25%) had chronic diseases.

Of the entire cohort, 47% were discharged to home isolation following their diagnosis, with the remainder being admitted to the hospital (45%) or a nursing facility (8.4%). The vast majority of patients (369; 89%) had only mild symptoms with no need for any respiratory support, however 32 (7.9%) patients received oxygen support, 18 (4.5%) were admitted to the intensive care unit, 17 (4.2%) were ventilated and 12 (3%) died. A total of 179 (44%) patients had fever during their disease. The most commonly used antipyretic was paracetamol (32% of the population), with 22% reporting using ibuprofen and 3.7% using dipyrone (Table 1).

Ibuprofen intake, mortality and respiratory support in COVID-19 patients

Patients who took ibuprofen at any time during the course of their disease had characteristics similar to those who did not receive ibuprofen except for the fact that 79% of patients using ibuprofen had fever, but only 35% of patients that avoided the use ibuprofen reported fever ($p < 0.001$).

In the ibuprofen group, 3 (3.4%) patients died, whereas in the non-ibuprofen group 9 (2.8%) patients died (p 0.95). Nine (10%) patients from the ibuprofen group needed respiratory support, compared with 35 (11%) from the non-ibuprofen group (p 1) (Table 1).

Ibuprofen versus paracetamol use in febrile COVID-19 patients

Patients with fever who used paracetamol or ibuprofen exclusively had similar age and gender.

No difference in mortality rates was observed (0 versus 3, p 0.3). One (2%) of the exclusive ibuprofen users needed any respiratory

Table 1
Characteristics of study participants

Characteristic	Overall	Without ibuprofen intake	With ibuprofen intake	p value	Proportion difference (%) (95% CI)
No. of participants	403	316	87		
Gender, female/male (%)	183/220 (45.4/54.6)	142/174 (44.9/55.1)	41/46 (47.1/52.9)	0.81	0.8 (−14.8 to 10.4)
Age (years), median (interquartile range)	45.00 (25.00, 62.00)	46.00 (25.00, 61.00)	40.00 (24.50, 64.00)	0.96	
Chronic diseases (%)	101 (25.1)	79 (25.0)	22 (25.3)	1	0.3 (−10.3 to 10.9)
Cardiovascular disease (%)	52 (12.9)	40 (12.6)	12 (13.7)	0.85	1.1 (−8.2 to 9.6)
Diabetes (%)	38 (9.4)	28 (8.8)	10 (11.4)	0.53	2.6 (−13.7 to 17.6)
Admitted				0.16	
No (%)	188 (46.7)	145 (45.9)	43 (49.4)		
Hospital (%)	181 (44.9)	148 (46.8)	33 (37.9)		
Nursing facility (%)	34 (8.4)	23 (7.3)	11 (12.6)		
Fever (%)	179 (44.4)	110 (34.8)	69 (79.3)	<0.001	44.5 (33.8−55.2)
Respiratory symptoms (%)	194 (48.1)	160 (50.6)	34 (39.1)	0.074	−11.5 (−23.9 to 0.8)
Observed clinical outcomes					
Received supplemental oxygen (%)	32 (7.9)	27 (8.5)	5 (5.7)	0.53	−2.8 (−9.3 to 3.7)
Mechanically ventilated (%)	17 (4.2)	13 (4.1)	4 (4.6)	>0.95	0.5 (−4.9 to 5.9)
Admitted to the intensive care unit (%)	18 (4.5)	13 (4.1)	5 (5.7)	0.72	1.6 (−4.5 to 7.7)
Administration of respiratory support (%)	44 (10.9)	35 (11.1)	9 (10.3)	>0.95	−0.8 (−8.7 to 7.3)
Died (%)	12 (3.0)	9 (2.8)	3 (3.4)	>0.95	0.6 (−4.3 to 5.5)

Statistics presented: *n* (%), median (interquartile range).
Statistical tests performed: chi-square of independence, Wilcoxon rank-sum test; Fisher's exact test.

Table 2
Febrile COVID-19 patients who exclusively used ibuprofen or paracetamol

Characteristic	Overall	Exclusive paracetamol intake	Exclusive ibuprofen intake	p value	Proportion difference in % (95% confidence interval)
No. of participants	134	85	49		
Gender Female/Male	60/74 (44.8/55.2)	41/44 (48.2/51.8)	19/30 (38.8/61.2)	0.4	9.4 (−9.4 to 28.3)
Age (years)	46.00 (24.00, 65.00)	48.00 (27.25, 67.00)	34.50 (23.25, 56.50)	0.09	
Administration of respiratory support	12 (9.0)	11 (12.9)	1 (2.0)	0.06	10.9 (0.3–103)
Died	3 (2.2)	3 (3.5)	0 (0.0)	0.3	−3.5 (−9.1 to 2)

Statistics presented: *n* (%), median (interquartile range).
Statistical test performed: chi-square of independence, Wilcoxon rank-sum test; Fisher's exact test.

support during their disease course, compared with 11 (12.9%) of the exclusive paracetamol users (p 0.06) (Table 2).

Discussion

In this retrospective cohort study of 403 individuals with COVID-19 admitted to Shamir Medical Centre in central Israel, we did not observe an increased risk for mortality or the need for respiratory support in patients treated with ibuprofen. Among patients with fever, no excess mortality or need for respiratory support was observed in those who chose to use ibuprofen exclusively. In fact, the need for respiratory support was higher in the paracetamol group with borderline significance. One possible explanation for this could be that elderly patients with more severe chronic illnesses are more likely to be treated with paracetamol because of concerns about ibuprofen causing renal injury.

Our study has several limitations. First, as with any retrospective study, recall-bias is a concern. However, given the relatively short time-frame included in the study we expect this to be of minor concern. Furthermore, this possible limitation should not favour one treatment over the other. Second, information from deceased patients could only be collected from medical chart review. However, medications administered before hospitalization are noted in the charts. Third, our sample size was not sufficient to allow multivariable analyses. Lastly, the policy of the Israeli Ministry of Health was to test only those individuals with symptoms that are suggestive of COVID-19. As a result, we have no information about ibuprofen in asymptomatic carriers, and whether antipyretics can influence their clinical course. A major strength of this study is the high response rate and nearly complete follow up of patients admitted to a tertiary hospital. The balanced representation of the different severities of the disease, compatible with the distribution of disease in the Israeli population, is another strength.

The claim that ibuprofen is unsafe for use in individuals with COVID-19 symptoms was raised in the early stages of the COVID-19 outbreak, following the observation that SARS-CoV-2 binds to its target cell through ACE2 in the lung [10]. This led to the hypothesis that ACE2-stimulating drugs, such as ACE inhibitors and ibuprofen, might increase the risk for severe and fatal COVID-19 disease [3]. Regarding ibuprofen, this hypothesis was not supported in our cohort. Larger prospective studies are needed to validate our results.

Transparency declaration

The authors report no conflict of interest.

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Authors' contributions

EK and IY conceptualized the study, IY, YS and ABH collected the data, IY and ER conducted the data analyses, ER wrote the first draft of the manuscript, IY and EK revised the manuscript, all authors approved the final version.

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