IBUPROFEN

RECOMMENDATION

We recommend against the use of ibuprofen as treatment in patients with COVID-19 infection. *(Very low quality of evidence; Strong recommendation)*

Consensus Issues

It is important to note that this recommendation is strictly for the use of ibuprofen in the treatment of COVID-19 infection and should not be confused with another living recommendation pertaining to the effect of the concurrent use of ibuprofen with other COVID-19 outcomes.
There is a trend towards benefit from the direct evidence which was of very low quality, however, there is an indirect evidence of possible harm. The benefit that was seen from the first study might not be solely because of ibuprofen given that other patients were given other medications. The severity of COVID-19 infection was not also specified in the first study and it was assumed that it included patients of all severity (i.e., mild, moderate, severe) since the information were taken from electronic health records of different hospitals.

EVIDENCE SUMMARY

Should ibuprofen be used in the treatment of patients with COVID-19 infection?

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Key Findings

Currently, there are no randomized controlled trials available about the efficacy of ibuprofen in the treatment of COVID-19. Based on the two observational studies included in this review, (one retrospective cohort and one case series) which were pre-prints and have not been peer-reviewed, there is limited evidence that ibuprofen treatment could improve COVID-19 symptoms and outcomes.

Introduction

The 2019-nCOV belongs to a family of viruses with positive-sense single stranded RNA genome with a lipid envelope in its structure. [1] Ibuprofen in vitro has demonstrated virucidal activity against enveloped viruses [2]. Several studies have demonstrated that non-steroidal anti-inflammatory drugs (NSAIDs) including ibuprofen can alter adherence, degranulation and

phagocytosis and production of reactive oxygen species (ROS) by polymorphonuclear neutrophils (PMNs). In addition to this, treatment with ibuprofen, flurbiprofen and indomethacin led to a significantly reduced migration of leukocytes and volume of exudates in acute pleural effusion [3-6]. Moreover, NSAIDs could also reduce local release of pro-inflammatory cytokines through the effect on cyclooxygenases [7-11]. Its anti-inflammatory effects led to the hypothesis that ibuprofen could aid in the treatment of cytokine storm.

Review Methods

Eligible articles were appraised using the Painless Evidence-Based Medicine book by Dans et al. evaluating directness, validity and applicability using the following:

Population	COVID-19 patients
Intervention/Exposure	Ibuprofen
Comparison	Usual standard of care or placebo
Outcomes	Clinical Improvement (i.e. decrease in hospitalization rate, decrease in duration of hospital stay, decreased oxygen requirement, decrease in mortality rate)
Methodological filter	Randomized controlled trials (RCT), observational clinical studies, systematic review and meta-analysis available, case series

Results

A retrospective cohort study done by Castro et al [12] identified common pharmacotherapies associated with reduced COVID-19 morbidity using electronic health records. They included 7,360 patients from six hospitals in Massachusetts, USA. Data of the patients including medication exposure were obtained from electronic health records in the one year to 30 days prior to presentation to the emergency department. The primary outcome was hospitalization among COVID-19 positive patients and the secondary outcomes were intensive care unit (ICU) admission and death among those COVID-19 patients who were hospitalized. After adjusting for age, sex, race, ethnicity, site and Charlson score, Ibuprofen was one of the prescribed medications associated with lower hospitalization rate (odds ratio (OR), 0.73; 95% confidence interval (CI), 0.64 to 0.84). Furthermore, ibuprofen was also associated with a significantly decreased odds of requiring ICU (OR, 0.70; 95% CI, 0.56 to 0.86), and mortality (OR, 0.73; 95% CI; 0.56 to 0.96). There was no report on the adverse events in the study. The observational nature of this study makes it difficult to ascertain if it was ibuprofen intake that caused such reductions in hospitalization, ICU admission and mortality. Patients were not randomized hence other confounders that could not be controlled could have led to these effects. Also, the investigators only extracted data through electronic health records and actual intake of the medications could not be assured. Moreover, they only noted intake of the medications from one

year to 30 days prior to the presentation and not while the patients were having COVID-19 infection. This study is a pre-print version and not peer reviewed.

A case series done by Kelleni et al. [13] included 17 COVID-19 confirmed or suspected Egyptian patients who were living in the Kingdom of Saudi Arabia (KSA). Among the 17 patients were 7 males, 5 females, 2 pregnant patients and 3 pediatric patients. The author used his own treatment protocol that includes nitazoxanide, azithromycin and ibuprofen or diclofenac which were given in different combinations as dictated by his own judgment. He also allowed some of the patients to have concurrent intake of vitamin C and zinc and any other food supplements. He classified all of these patients as improved however, there was no specific criteria for the improvement in symptoms and he based it on patients' subjective feeling of improvement as well as lysis of fever, resolution of sore throat, dyspnea, cough and diarrhea. He also noted improvement in the lymphocyte and neutrophil counts. In this case series, there was no report of adverse drug reactions. This study has a lot of biases. This is a non-randomized controlled study hence the improvement noted in these patients could just be due to chance. Patients included in the study seemed to have mild to moderate severity of infection and they could have improved even without giving the medications. The exposure to treatment was also based on the author's judgment. In addition to this, the patients and the outcome assessor which is also the author were not blinded so there could also be performance bias and observer bias. The author included patients who were not tested for COVID-19 and just assumed that they were infected based on exposure and symptoms so we cannot ascertain if they really had COVID-19 infection. Also, there was no individual description of cases written in the report. This study is a pre-print version and not peer reviewed

Indirect evidence for harm

A systematic review was done by Philipsborn et al among patients with viral respiratory infection exposed to NSAIDs. Studies on patients of any age, with viral respiratory infections or conditions commonly caused respiratory viruses and exposed to systemic NSAIDS of any kind reporting on acute severe adverse events, acute healthcare utilization, explicit quality of life measures and long term survival were included. They searched MEDLINE, EMBASE, WHO-COVID Database, Scopus and references of existing reviews and included studies. A total of 87 eligible studies were included (72 RCTs, 7 cohort, 3 case-cross-over studies, 3 non RCTs, 1 case-control study and 1 case series) with a total of 172,831 patients and median follow up of 3 days. They were not able to identify any study on COVID-19, SARS of MERS meeting the eligibility criteria. Data extraction and quality assessment of included studies were done by one author only. They used tools Assess Risk of Bias for Case Control Studies, Cochrane risk of Bias tool and GRADE. In one included retrospective cohort study among 683 adults, the effects of NSAID on mortality in critically ill adults with influenza during the 2009/2010H1N1 influenza pandemic are unclear (adjusted RR (aRR): 0.9, 95%CI: 0.5 to 1.6). The confidence interval is wide and includes the possibility of a negative, null or positive effect. This evidence was graded as very low certainty. Two case cross-over studies in 9793 patients with myocardial infarction and 29,518 patients with ischaemic or haemorrhagic stroke assessed effects on cardiovascular events, and showed higher ORs for the combined exposure to NSAIDs and acute respiratory infection than acute respiratory or NSAIDs alone. For ischemic stroke, the risk associated with NSAID use and ARI episode reported

aOR=2.27 (95% CI: 2.00 to 2.58); for hemorrhagic stroke it was aOR=2.28 (95% CI: 1.71 to 3.02), and for myocardial infarction the risk associated with NSAID use and ARI episode was aOR=3.41 (95% CI: 2.80 to 4.16). Other adverse events noted in 28 RCTs and two cohort studies included nausea, dyspepsia, urticaria, syncopation, pneumonia, meningitis, peritonsillar abscess, abdominal pain, drowsiness and lightheadedness. Among critically-ill children with H1N1 influenza, there was an unclear effect of NSAIDs on mortality (aRR 1.5, 95% CI: 0.7 to 3.2; very low certainty evidence). Other adverse events noted among children with viral respiratory infection given NSAIDs were empyema and gastrointestinal bleeding. This study has not been peer-reviewed. This was considered indirect evidence because the patients in this study had other viral respiratory infections and not COVID-19. In addition to this the exposure of interest was NSAID in general and not ibuprofen. As to reproducibility, only one author did the data extraction and quality assessment. There is also a note of selection bias because they only included articles with study designs most capable of detecting rare severe adverse events. There is also channeling bias in the studies included wherein patients who are critically ill and with more severe symptoms were more likely to be given NSAIDS which could have contributed to the results.

There were no RCTs found in the search but only two observational studies which were pre-print and not peer reviewed. One systematic review on the use of ibuprofen on patients with viral respiratory infection included showed possible harm. This was considered indirect because the study did not include patients with MERS, SARS and COVID. The results of these studies were of very low certainty.

Recommendations from Other Groups

Currently there are no clinical practice guidelines that recommend the use of ibuprofen as treatment for COVID-19.

Research Gaps

Ongoing clinical trials are shown on Appendix 4.

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Appendix 1: Characteristics of Included Studies

Author, Year	Patients (n)	Intervention	Comparator	Outcomes
Castro et al, 2020	COVID-19 confirmed patients (n=7,360)	Pharmacotherapies identified to be used among patients with COVID-19 including iburpofen	no Ibuprofen	Ibuprofen was one of the prescribed medications associated with lower hospitalization rate (odds ratio (OR), 0.73; 95% confidence interval (CI), 0.64 to 0.84). Furthermore, ibuprofen was also associated with a significantly decreased odds of requiring ICU (OR, 0.70; 95% CI, 0.56 to 0.86) and mortality (OR, 0.73; 95% CI; 0.56 to 0.96).
Kelleni et al. 2020	COVID-19 patients confirmed/suspected n=17)	Nitazoxanide/Azithromycin/Ibuprofen or diclofenac	none	There was note of improvement and decrease in duration of symptoms. There was an increase in lymphocyte counts and decrease in neutrophil count

Appendix 2: GRADE Evidence Profile

Summary of findings:

Ibuprofen compared to Placebo or usual care for COVID-19

Patient or population: COVID-19
Setting:
Intervention: Ibuprofen
Comparison: Placebo or usual care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Placebo or usual care	Risk with Ibuprofen				
Hospitalization follow up: 4 months	527 per 1,000	**449 per 1,000** (417 to 484)	**OR 0.73** (0.64 to 0.84)	7360 (1 observational study)	⨁◯◯◯ VERY LOW [a,b]	
ICU admission	0 per 1,000	**0 per 1,000** (0 to 0)	**OR 0.70** (0.56 to 0.86)	7360 (1 observational study)	⨁◯◯◯ VERY LOW [a,b,c]	
Mortality	0 per 1,000	**0 per 1,000** (0 to 0)	**OR 0.73** (0.56 to 0.96)	7360 (1 observational study)	-	
Resolution of symptoms	All patients improved			17 (1 observational study)	⨁◯◯◯ VERY LOW [d,e]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **OR:** Odds ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. The data were extracted only from electronic health record hence actual intake of medications were not assured. No mention on the severity of cases and the reasons for admission were based only on the physicians' clinical judgment. They did not indicate whether the exposure to medication was during the time when the patients were infected with COVID-19.
b. the exposure to the medication was 1 year to 30 days prior to the patient presenting at the emergency department
c. Confounding by indication
d. The author combined ibuprofen with other medications, no strict protocol with regards to treatment which the author based on his own judgments. Patients and outcome assessors were not blinded
e. the author included patients who were not confirmed cases of COVID-19 (i.e. no RT PCR done and only based it on symptoms plus exposure of patients

Summary of Findings Table (Indirect Evidence)

Outcomes	Effect Estimate	95% Confidence Interval	Basis	Certainty of evidence
Mortality	RR, 0.90	0.50 to 1.60	1 retrospective registry based cohort study (683)	Uncertain, Very Low[ab]
Ischemic Stroke	RR, 2.27	2.00 to 2.58	1 case-crossover study (23,618)	Harmful, Very Low[ab]
Hemorrhagic Stroke	RR, 2.28	1.71 to 3.02	1 case-crossover study (5,900)	Harmful, Very Low[ab]
Myocardial infarction	RR, 3.41	2.80 to 4.16	1 case-crossover study (5,900)	Harmful, Very Low[ab]

a. studies included for this comparison were non randomized
b. downgraded by 1 level for imprecision

Appendix 4. Characteristics of Ongoing Studies

Clinical Trial Identifier/Title	Study Design	Country	Population	Intervention	Outcome
NCT04500639 Do Common Medications Alter the Course of COVID-19?	Observational, Case Control Propective Study	Canada	Patients tested for COVID-19	not provided	Ibuprofen exposure for symptom management
NCT04382768 Extended Compassionate Use Program (UCA) With Inhalational Ibuprofen in Patients With Acute Respiratory Pathology, Mediated by COVID-19	Interventional Open label Single group Assignment	Argentina	Patients with COVID-19	Inhaled ibuprofen and standard of care plus lipid ibuprofen 200mg	Primary outcome: 1. Time to clinical improvement 2. Change to Negativization of the swab Secondary Outcome: 1. Change in length of hospital stay 2. duration of ventilation 3. critical care stay 4. Average score in National Early Warning (NEWS2) 5. Time from first dose to conversion to normal or mild pneumonia 6. Antibiotic requirement 7. Glucocorticoids requirement 8. Incidence of adverse event 9. Incidence of serious adverse event 10. Number of deaths from any cause at 28 days 11. Lymphocyte count
NCT04334629 Lipid Ibuprofen Versus	Randomized, double blind,	United Kingdom	Adult patients with confirmed	Ibuprofen and Standard of Care	Primary Outcome: 1. Disease Progression

Standard of Care for Acute Hypoxemic Respiratory Failure Due to COVID-19: a Multicentre, Randomised, Controlled Trial (LIBERATE)	parallel assignment		COVID-19 infection		2. Time to Mechanical Ventilation Secondary Outcome: 1. Overall survival 2. Reduction in proportion of patients who require ventilation 3. Reduction in length of Critical Care stay 4. Reduction in length of Hospital stay 5. Modulation of serum pro- and anti-inflammatory cytokines 6. Reduction in duration of ventilation 7. Increase in ventilator-free days
NCT04383899 Role of Ibuprofen and Other Medicines on Severity of Coronavirus Disease 2019 (COVID-19) Infections: a Case-control Study	Case Control	France	Patients with COVID-19	Case and Control using a questionnaire	Describe and quantify medications used prior to admission associated with worse infection in COVID-19