IBUPROFEN

RECOMMENDATION

We suggest that Ibuprofen may still be used as symptomatic treatment of patients with COVID-19 infection if clinically warranted. Concurrent use of ibuprofen is not associated with worsening of COVID-19 outcomes. *(Very low quality of evidence; Conditional recommendation)*

Consensus Issues

There were no issues raised during the consensus panel meeting.

EVIDENCE SUMMARY

Does the concurrent use of Ibuprofen worsen COVID-19 outcomes?

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Key Findings

There has been concern on the use of ibuprofen in COVID-19. Fang et al. reported that the point of entry for SARS-COV-2 is through angiotensin- converting enzyme 2 receptor, which is believed to be upregulated by ibuprofen. Based on six observational studies assessed, there was no significant association between ibuprofen use and worse COVID-19 outcomes: composite outcome (death, acute respiratory distress syndrome, ICU admission, shock) OR, 1.06 (95% CI; 0.81 to 1.40), Death OR, 1.07 (95% CI; 0.35 to 3.24), and progression of symptoms after propensity score matching. Five clinical trials on Ibuprofen use in COVID-19 are still on-going.

Introduction

One of the most common symptoms of COVID-19 is fever [1] and among the most frequently used antipyretic agents is ibuprofen. There has been concern with regards to the use of ibuprofen in COVID-19 [2,3]. On March 11, 2020, The Lancet published an article based on the observation by Fang et al. that SARS-COV-2 point of entry for its pathogenesis is through angiotensin-converting enzyme 2 receptor, which is believed to be upregulated by ibuprofen [4]. However, the World Health Organization and the European Medicines Agency (EMA) released a statement that there is currently no direct scientific evidence to support this claim and advised against avoidance of ibuprofen as treatment of fever if it is clinically warranted [5,6]. A systematic review by Yousefifard et al. including six studies failed to associate NSAID intake with worsened outcomes among patients with viral respiratory infections although none of these trials have been performed on COVID-19, SARS or MERS-CoV [7]. Furthermore, among adult patients with acute respiratory

infection, the effects of NSAIDs on the risk for ischemic and haemorrhagic stroke and myocardial infarction are unclear [8-9]. There is little or no evidence that ibuprofen increases death from all causes, hospitalization for any cause, acute renal failure, and acute gastrointestinal bleeding among children with fever compared with paracetamol [10-11].

Review Methods

We performed a comprehensive systematic search of the literature from two electronic databases, Medline and CENTRAL. We also searched for ongoing clinical trials using ClinicalTrials.gov and Clinicaltrialsregister.eu. We did freehand search using Google to check for other sources of information, including the Love Platform App. Search was conducted using the following search terms: COVID-19, SARS-CoV-2, ibuprofen and non-steroidal anti-inflammatory agents.

Eligible articles were appraised using accepted standard processes evaluating directness, validity, and applicability using the following:

Population	COVID-19 patients
Intervention/Exposure	Ibuprofen
Comparison	Paracetamol; No ibuprofen use
Outcomes	Increased risk of infection, worsening of symptoms, increase in severity of symptoms or death
Methodological filter	Randomized controlled trials (RCT), observational clinical studies, systematic review and meta-analysis available, case series

Results

A total of six observational studies met the inclusion criteria and were included in this review. There were five cohort studies and one cross-sectional study. All studies included COVID-19 confirmed patients by RT-PCR given ibuprofen for symptomatic relief of fever and pain.

A prospective cohort study [12] looked into several risk factors for disease progression including the impact of drugs such as (angiotensin II receptor blockers [ARB], ibuprofen, and dipeptidyl peptidase-4 inhibitors [DPP4i]) and the therapeutic effect of lopinavir/ritonavir. They included patients with confirmed COVID-19 infection by RT-PCR from March 5-18, 2020 with final follow up on April 4, 2020. The outcome was classified into either disease progression or improvement/stabilization group. They conducted a propensity-score matched case-control study to control for possible confounding variables using the result of the univariable analysis. After PS-matching, prior history of drug use, including ibuprofen, ARB, DPP-4i was not statistically significant. The effect of these drugs on prognosis did not significantly differ in patients with hypertension and diabetes mellitus. However, the retrospective, single center and limited number of patients in the progression group (30 vs 263) may limit the wider applicability of the result. Moreover, other potential hidden biases and confounding factors not controlled by propensity score matching might have influenced the results.

Another prospective cohort study done by Esba et al, 2020 [13] aimed to assess the association of acute and chronic ibuprofen use of NSAIDs with worse COVID-19 outcomes. A total of 503 patients with confirmed COVID-19 infection were included in the study from April 12 to June 1, 2020. Information of ibuprofen or NSAID use was collected using a telephone questionnaire. The primary outcome was 30-day mortality and the secondary outcomes were severe COVID-19

infection, hospital admission and for admitted patients time to clinical improvement, oxygen support, and length of hospital stay. After adjusting for covariates, results showed that acute ibuprofen use was not associated with a greater risk of mortality HR 0.63 (95% CI, 0.07-5.44; p=0.68). It was also not significantly associated with mortality (RR 2.70; (95% CI, 0.33 – 22.00) p=0.35), risk of admission (RR 1.18 (95% CI, 0.59–2.36) p=0.64), oxygen support (RR 1.45 (95% CI, 0.44–4.81) p=0.55), and severe COVID-19 (RR 1.85 (0.42–8.13) p=0.42). Being an observational study, causal relationship between ibuprofen use and severe outcomes could not be established. Moreover, there could be selection bias with regard to recruitment since the study was done at the early stage of the pandemic. There could also be recall bias since the respondents were asked through a telephone questionnaire.

An observational retrospective cohort study by Kraghold et al [14] assessed the association of prescribed ibuprofen and severe covid-19 infection. They included 4,002 COVID-19 confirmed patients, 264 of which filled ibuprofen prescriptions. Data were obtained using the Danish National Prescription Registry for ibuprofen prescription claims and identified COVID-19 positive patients using the Danish National Patient Registry. The two groups, ibuprofen and non-ibuprofen COVID-19 patients, were standardized by age, sex, and co-morbidity distribution using the multivariate Cox regression. The outcome of interest was the 30-day composite of acute respiratory syndrome, intensive care unit admission, or death. Results showed that there was no statistical difference between the ibuprofen and non-ibuprofen groups with regard to the 30-day composite outcome with absolute and average risk ratios of 16.3% (95% confidence interval (CI) 12.1–20.6) vs. 17.0% (95% CI 16.0–18.1), P = 0.74 and 0.96 (95% CI 0.72–1.23) respectively. The standardized absolute risks of the composite outcome for patients with ibuprofen prescription claims >14 days before COVID-19 and <14 days of COVID-19 were 17.1% (95% CI 12.3–22.0) vs. 14.3% (95% CI 7.1–23.1). They found no significant association between ibuprofen prescription claims and severe COVID-19. However, given the retrospective and observational nature of the study causal relationship could not be established. The study also did not look into individual outcomes or whether ibuprofen use had an effect on each of them. Filling prescription claims does not translate to patients actually taking ibuprofen. Also, they were not able to find out if ibuprofen was continued even during admission.

In one retrospective cohort study that evaluated the clinical outcomes among patients with COVID-19 taking NSAIDS [15], NSAID use was ascertained using patients' electronic medical records. The primary outcome was a composite of death, respiratory failure requiring intubation, and shock requiring vasopressors, occurring within 28 days of ED presentation. After controlling for other variables such as co-morbidities and use of other medications, they found out that NSAID use was not an independent predictor of critical COVID-19 illness (odds ratio 0.05 (95% CI; -0.57 - 0.73). This is a retrospective cohort study and no causal relationship could be established. There was no mention in the paper which type of NSAIDS the patients were taking.

The retrospective cohort study of Rinott et al [16] is among patients with confirmed COVID-19 infection done in Israel from March 15 to April 15, 2020 aimed to evaluate whether the administration of ibuprofen to COVID-19 patients was associated with worsened clinical outcome compared with paracetamol or no antipyretic. They collected data through telephone questionnaire (mean 13 days after diagnosis, range 2-30 days) including information about 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) and intake of ibuprofen or paracetamol or dipyrone 1 week prior to diagnosis. Severe disease was defined as needing any respiratory support (supplemental oxygen administration or ventilation), admission to intensive care unit or death. A total of 403 confirmed cases were included in the study. Using Chi square test of independence, Wilcoxon Rank – Sum test and Fischer's Exact test, the authors found no statistically significant difference between

"without Ibuprofen intake" group and "with ibuprofen intake" group in terms of receiving supplemental oxygen (8.5% vs 5.7% p=0.53), being mechanically ventilated (4.1% vs 4.6% P>0.95), admission to ICU (4.1% vs 5.7% p=0.72), administration of respiratory support (11.1% vs 10.3% P>0.95), and death (9% vs 3% p>0.95). Also, when exclusive ibuprofen group was compared with exclusive paracetamol group in terms of death, there was also no statistically significant difference between the two groups (0% vs 3% p=0.3). This study had a lot of biases. They did not consider to control possible confounders in the study. There could also be a recall bias since patients were asked through telephone questionnaire.

A cross-sectional study done by Samimagham et al [17] included 158 patients with confirmed COVID-19 infection who consumed ibuprofen for at least 1 week in the past 3 months. The patients were grouped into mild, moderate and severe groups. In this study, they found out that there is a significant relationship between ibuprofen consumption and severity of the disease (p<0.001). After adjustment, there was a statistically significant relationship between ibuprofen consumption and mortality among patients with COVID-19 (OR; 2, p=0.001). This is a cross-sectional study design where neither temporal association nor causation could be established. There could also be channeling bias wherein ibuprofen was given to patients who had more severe symptoms since it has a more potent anti-inflammatory property than paracetamol. The outcome was biased especially the intensive care unit (ICU) admission because there was no strict criteria for admission and instead it depended on the judgment of the attending physician. There is also a question on generalizability of the study since it only included 158 patients.

All of the studies included confirmed COVID-19 patients by RT-PCR with no specific severity. In 3 studies, the exposure to ibuprofen was during the infection whereas in the other 3 studies, the exposure was prior to the infection. Only one study described the dose given to patients. Most of these studies used EMR and telephone questionnaire to gather data.

Recommendations from other groups

The World Health Organization (WHO) and the European Medicines Agency (EMA) released a statement that there is currently no direct scientific evidence to support that ibuprofen could worsen COVID-19 and does not recommend against the use of ibuprofen as treatment of fever if it is clinically warranted [5,6]

Ongoing Studies

There are five ongoing clinical trials (shown on Appendix 3)

References

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Appendix 1: Characteristics of Included Studies

Author, Year	Patients (n)	Intervention	Comparator	Outcomes	Study Design
Choi et al, 2020	COVID-19 confirmed patients(n=293)	the impact of drugs (angiotensin II receptor blockers [ARB], ibuprofen, and dipeptidyl peptidase-4 inhibitors [DPP4i]) and the therapeutic effect of lopinavir/ritonavir.	Propensity score – matching control	No statistical difference between the progression and improvement/stabilization group when it comes to ibuprofen use 6 vs 2 p 0.261, after propensity score matching, ibuprofen 6 vs 6 p >0.99, For risk for progression free survival using Cox Regression Analysis OR, 2.72; (1.13 – 6.24) p 0.025	Retrospective Cohort, propensity score matched case control
Esba et al. 2020	COVID-19 confirmed patients(n=503)	Ibuprofen or other NSAID use	Non Ibuprofen/NSAID users	After adjustment for covariates, results showed that acute ibuprofen use was not associated with a greater risk of mortality HR 0.632 (95% CI, 0.073-5.44; P=0.6758). It was also not associated with mortality, risk of admission, oxygen support, and severe COVID-	Observational, Prospective cohort study

Author, Year	Patients (n)	Intervention	Comparator	Outcomes	Study Design
				19 with fully adjusted RR 2.6951; (95% CI, 0.3302 – 21.9964) P=3547 (mortality), RR 1.1.1819 (95% CI, 0.5917–2.3606) P=0.6359 (admission), RR 1.4482 (95% CI, 0.4361–4.8089) P=0.5454 (oxygen support) and RR 1.8484 (0.4202–8.1314) P=4163 (severe COVID-19).	
Kragholm et al., 2020	COVID-19 confirmed patients(n=4,002)	Prescribed Ibuprofen	Non-Ibuprofen	no statistical difference between the ibuprofen and non-ibuprofen groups when it comes to the 30 day composite outcome with absolute and average risk ratios of 16.3% (95% confidence interval (CI) 12.1–20.6) vs. 17.0% (95% CI 16.0–18.1), OR 0.91;(95% CI; 0.64-1.27) P = 0.74 and 0.96	Retrospective Cohort

Author, Year	Patients (n)	Intervention	Comparator	Outcomes	Study Design
				(95% CI 0.72–1.23) respectively.	
Perkins et al, 2020	COVID-19 confirmed patients(n=422)	NSAID users	Non NSAID users	NSAID use was not found to be an independent predictor of critical COVID-19 illness (odds ratio = 0.05 (95% CI; -0.57 - 0.73)	Retrospective cohort study
Rinott et al., 2020	COVID-19 confirmed patients(n=403)	Ibuprofen intake	No antipyretic or paracetamol	no statistically significant difference observed between the without Ibuprofen intake and with ibuprofen intake in terms of receiving supplemental oxygen 8.5% vs 5.7% P=0.53, mechanically ventilated 4.1% vs 4.6% P>0.95, admission to ICU 4.1% vs 5.7% P=0.72, administration of respiratory support 11.1% vs 10.3% P>0.95 and	Retrospective cohort study

Author, Year	Patients (n)	Intervention	Comparator	Outcomes	Study Design
				death 9% vs 3% P>0.95. Also when exclusive ibuprofen group was compared with exclusive paracetamol group in terms of death, there was also no statistically significant difference between the two groups 0% vs 3% P=0.3	
Samimaghal et al. 2020	COVID-19 confirmed patients(n=158)	Ibuprofen	Non-ibuprofen	significant relationship between ibuprofen consumption and severity of the disease with a P<0.001. After adjustment of the odds ratio 2, P=0.001 there was a significant relationship between ibuprofen consumption and mortality among patients with COVID-19	Cross sectional

Appendix 2: GRADE Summary of Findings (SoF) table

Summary of findings:

Ibuprofen compared to usual standard of care/paracetamol for COVID-19

Patient or population: COVID-19
Setting:
Intervention: Ibuprofen
Comparison: usual standard of care/paracetamol

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with usual standard of care/paracetamol	Risk with Ibuprofen				
Composite Outcome (Death, ARDS, ICU, Shock)	193 per 1,000	**203 per 1,000** (163 to 251)	**OR 1.06** (0.81 to 1.40)	4582 (3 observational studies)	⨁◯◯◯ VERY LOW [a,b,c]	
Death	30 per 1,000	**32 per 1,000** (11 to 90)	**OR 1.07** (0.35 to 3.24)	800 (2 observational studies)	⨁◯◯◯ VERY LOW [a,c]	
Progression of Symptoms	After PS matching, Ibuprofen was not associated with progression of symptoms among COVID-19 patients			293 (1 observational study)	⨁◯◯◯ VERY LOW [a,c]	

***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. interviewer bias, measurement bias, recall bias and channeling bias
b. The study of Samimagham had different results compared with the other two
c. The exposure in 1 study was prior to the diagnosis of COVID-19

Appendix 3: Characteristics of Ongoing Studies

Clinical Trial Identifier (Location)	Official Title	Methodology	Groups	Estimated Date of Completion
NCT04500639	Do Common Medications Alter the Course of COVID-19?	Observational, Case Control Propective Study	Not provided	Dec 31, 2020
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	Experimental: Luarprofen Inhaled Hypertonic Ibuprofen 50mg TID \	January 2021
NCT04334629	Lipid Ibuprofen Versus Standard of Care for Acute Hypoxemic Respiratory Failure Due to COVID-19: a Multicentre, Randomised, Controlled Trial (LIBERATE)	Randomized, double blind, parallel assignment	Experimental: Lipid Ibuprofen No intervention: Standard of Care	May 25, 2021
NCT04383899	Role of Ibuprofen and Other Medicines on Severity of Coronavirus Disease 2019 (COVID-19) Infections: a Case-control Study	Case Control	Case: severe COVID patients Control: Non severe COVID patients	Oct. 31, 2020

Clinical Trial Identifier (Location)	Official Title	Methodology	Groups	Estimated Date of Completion
2020-001203-16	Lipid ibuprofen versus standard of care for acute hypoxaemic respiratory failure due to COVID-19: a multicentre, randomised, controlled trial	Randomized, double blind, parallel assignment	Experimental: Lipid Ibuprofen No intervention: Standard of Care	May 25, 2021