

Mini Review

Rescue Therapy in Covid-19: NSAIDs and Mineralocorticoid Receptor Antagonists (MRBs)

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Abstract

Misleading claims about NSAIDs in early stage of Covid-19 pandemic resulted in a human and economic worldwide disaster.

We would like to claim that although SARS- CoV2 looks intractable but it is easily manageable as a common cold.

Combination of NSAIDs and Mineralocorticoid receptor antagonists (MRBs) and Cold Stop subsides Covid-19 in 72 hours.

Keywords: Covid-19 invasion; Ibuprofen; Javid protocol; Lipid emulsion; Mineralocorticoid receptor blocker; NSAIDs, Rescue therapy; Spironolactone

Introduction

What was the origin of the widespread rumors about adverse accelerating effects of NSAIDs in Covid-19?

“In March 14th concern was expressed by France’s Health Minister, Olivier Veran, in a tweet that suggested anti-inflammatory drugs, such as ibuprofen and cortisone could be an aggravating factor in people with COVID-19” [1].

“On the same day, the French government reported that NSAIDs, the family of drugs that include ibuprofen, were linked with “grave adverse effects” in patients affected by Covid-19” [1].

On March 19, FDA announced “FDA is not aware of scientific evidence connecting the use of NSAIDs, like ibuprofen, with worsening Covid-19 symptoms [1].

The medical University of Vienna released a statement declaring that “no research had taken place in this regard and that the text and voice messages were “fake news” [2].

Hydroxychloroquine was recommended to use with no scientific document. In comparison to such a dangerous and unsafe drug, especially in elderly patients who are at risk victims of Covid-19, NSAIDs could really be recommended as safe choice for restricting inflammatory reaction of the body against Covid-19 invasion.

It is questionable that why Hydroxychloroquine, such a dangerous and inefficient drug was not reported as harmful?

We would like to claim that not only NSAIDs are not harmful in Covid-19 but also, they are necessary as part of therapeutic medications to control inflammatory process in Covid-19 patients. As reported by author in April 2020, “NSAIDs play outstanding therapeutic role in early restriction of Covid-19 destructive complications through down regulating IL-6 production and suppressing PGE2 production (anti-inflammatory role)” [3].

Till now no approved curative or preventive protocol has been reported against Covid-19 and SARS CoV2 continues to fall victim to the world. Treatment with antiviral drugs has been failed and

maintenance therapies are preferred to inefficient harmful protocols.

To achieve the best therapeutic regimen for such a mysterious virus, we need to review the Covid-19 behavior in the body.

As soon as the virus enters to the body, an inflammatory reaction starts. Inflammatory reaction is an alarm system to restrict viral invasion. Inflammatory reaction is the primary reaction to harmful stimuli aroused from the mysterious Covid-19 invasion. In fact, inflammation is the body response to noxious stimuli such as damaged cells, irritants or pathogens. Positive CRP as one of the markers of choice in monitoring the acute phase response in Covid-19 patients has been mentioned as an indicator for inflammatory reaction in early stages of disease [4,5].

Acute progression of inflammation and increased inflammatory mediators’ result in suppressing immune system. Impaired immune system is accompanied by increased viral invasion and more inflammation. Final result is viral dominance and patients’ organ failure and mortality. Disruption of inflammatory process is necessary at early stage, while the immune system is efficacious enough to regress viral proliferation.

There is no documented evidence of infectious indicators in Covid-19 pulmonary complication in early stage. It might be better to change our attitude about infectious characteristic of Covid-19. It looks an inflammatory disease than an infectious one. Early suppression of inflammatory phase subsides activation of infectious process related to immunosuppressive mediators. This is the author’s hypothesis based on nonsystematic trial on 20 volunteer patients by combination of ibuprofen and spironolactone and cold-stop with surprising results after 72 hours [6].

Besides, regarding the hypothesis of non-infectious characteristics of Covid-19 complications, [6] and dominance of inflammation, NSAIDs are of value in this regard. In fact, inflammation is responsible for morbidity and mortality of Covid-19 invasion.

Increasing level of inflammatory mediators such as CRP, proposes early administration of anti-inflammatory medications. NSAIDs have a known practical anti-inflammatory effect in acute and chronic

inflammations.

Spironolactone is the second key medication in Covid-19 mysterious disease. Corona virus affects ACE, as portal of entry in cardiopulmonary system by binding to the cellular receptors through spike glycoproteins (viral S proteins). Spironolactone, a known ACE modulating drug, has been proposed as a good choice against Covid-19 invasion [3].

Mechanisms by which spironolactone prohibits viral invasion

Cytokine production, inflammation and cell damage is the result of all respiratory viral infections [7].

Viral invasion disrupts antioxidant mechanisms. Any kind of oxidative stress or imbalance between the production of Reactive Oxygen Species (ROS) and their elimination by protective mechanisms is accompanied by inflammation and cell damage [8].

Aldosterone is a steroidal stress hormone and specifically binds to the Mineralocorticoid Receptor (MR). Aldosterone has a pro-inflammatory immune effect. Release of pro-inflammatory cytokines, induction of oxidative stress and producing fibrosis and end organ damage is the result of aldosterone dominance [9,10].

Prevention of aldosterone binding to Mineralocorticoid receptors, exerts an anti-inflammatory effect.

Spironolactone as a Mineralocorticoid Receptor Blocker (MRB) with high affinity to aldosterone reduces oxidative stress and consequently reduces inflammatory reaction by virus [9,11].

Spironolactone molecule has 60% to 90% bioavailability and high affinity to proteins (88% Protein binding) [12]. Theoretically it can be bonded to spike proteins as soon as the virus enters to the circulation and prohibits viral achievement to cardiopulmonary system. It might be another probable mechanism of action in Covid-19.

We believe that Covid-19 is an inflammatory disease than an infectious one and administration of NSAIDs and aldosterone antagonists, have a protective and restrictive role in opposition to SARS CoV2 invasion. Early management of inflammatory reaction by proposed combination therapy attenuates the severity of complications and diminishes the period of the disease remarkably.

In the case of severe cardiopulmonary involvement in which the body is encountered with viral invasion and in other words viral intoxication, administration of intravenous lipid emulsion (intralipid) and packed cell is lifesaving as reported in the literature [6].

Using NSAIDs in combination to aldosterone inhibiting drugs and immune system supporting herbals has been proposed by author on March 24 as part of a preventive and therapeutic protocol against Covid-19 [7]

The proposed protocol and related proposals were evaluated as non-ethical by research department of Covid-19, in my country, may be because of the rumors and fake news about ibuprofen (part of the protocol) as mentioned above but the protocol was used in 20 volunteer patients by whom I was consulted.

We found outstanding successful therapeutic results. In all patients, symptoms such as fever, cough and dyspnea subsided in 72

hours and recovery occurred in one week. Treatment was continued for 10-14 days.

Cold-stop is administered as an adjuvant for pain management. Pain relief prevents prostaglandin production and consequently reduces releasing inflammatory mediators. Then cold-stop helps to reduce the recovery time.

Here I would like to share an easy, simple and low-cost protocol for prevention and rapid treatment of Covid-19 as below:

“Javid” protocol for treatment of Covid-19

The protocol includes two phases:

- **Prevention protocol:** It means prevention before getting involved with Covid-19 invasion (no symptom)
- **Treatment protocol:** It means treatment after manifestation of symptoms of Covid-19 invasion

Treatment Phase includes two stages:

- Treatment of Covid-19 invasion.
- Treatment of complications of the Covid-19 such as cardiopulmonary complications, CNS complications and other systemic involvements.

Prevention protocol

- Disinfection of nose, mouth, pharynx, face, hands and surfaces, furniture, instruments and so on by antiviral disinfectant if available (disclosed in patent application number: 62991333, USPTO) or any other disinfectant available.
- Drinking Chamomile tea (5 gm in 200 ml hot water as brewed or boiled for 2-3 minutes) twice a day or drinking Chamomile tincture 10-20 drops in a glass of water daily.
- Daily intake of Vitamin C 500 -1000 mg per oral.

Treatment protocol for home care in patients with mild illness

Providing care at home is recommended:

As soon as any symptom of Covid-19 erupted, treatment should be started through protocol below:

Besides continuation of preventive protocol mentioned above, immediate initiation of treatment is necessary, especially in patients with underlying chronic disorders such as lung or heart disease, renal failure or immune compromising conditions in order to prevent threatening and/or lethal complications as below:

- Tab Ibuprofen 400 mg TDS (about every 8 hours) in adults, and syrup Ibuprofen 5 ml (dessert spoon) TDS (every 8 hours) in children. In moderate to severe illness, this dosage can be increased by 2-3-fold, based on the severity of symptoms.
- Tab Spironolactone (Aldactone) 25 mg BD (about every 12 hours) in adults. In moderate to severe illness this dosage can be increased by 2-3-fold, based on the severity of symptoms.

It should be mentioned that in patients with chronic renal dysfunction and in combination to any other ACE inhibitor therapy the patient should be monitored for Hyperkalemia and should be

checked at least weekly.

In children spironolactone dosage is 1-3 mg/kg once or twice a day, based on the severity of illness.

- Tab Adult Cold or Cold Stop 1- 2 Tab TDS (about every 8 hours) based on the severity of illness.
- In children: syrup children cold 2.5 ml to 5 ml, TDS (about every 8 hours).
- In the case of anxiety, Tab Chlordiazepoxide 5 mg to 10mg twice a day. It could be substituted by other tranquilizers.
- In the case of nausea and vomiting, antiemetics such as metoclopramide and ondansetron in approved doses should be administered.

Treatment in hospitalized patients

In patients in whom no mechanical ventilation support is needed, besides the above proposed protocol, inhalation of chamomile tincture 1% through nebulizer for 10 minutes 2-3 times a day is recommended.

Treatment in deteriorating patients and in patients under mechanical support (ICU Admitted patients)

- Oral proposed protocol should be administered by gavage through nasogastric tube or intravenous administration if the drug is available for IV injection.
- Early administration of packed cell in patients with Hg<12 mg/dl to achieve this minimum requirement for maintaining enough oxygen delivery to vital organs and maintaining O₂ saturation.
- Early administration of parenteral amino acids according to standard approach for acute respiratory distress syndrome or systemic inflammatory response syndrome.
- Early administration of lipid emulsions according to standard approach for acute respiratory distress syndrome or systemic inflammatory response syndrome.

- Administration of IVIG according to standard dosage in immunoglobulin therapy in immunoglobulin deficient patients.

Treatment with all the above proposed protocol should be continued one week after complete subsiding of symptoms.

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