



Indomethacin for refractory COVID or post-COVID headache: a retrospective study

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Received: 10 June 2021 / Accepted: 26 August 2021 / Published online: 21 September 2021
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Abstract

Background COVID-19, a disease caused by SARS-CoV-2, manifests with headache, both in the acute phase and as a post-infection symptom, which may be refractory to usual analgesics.

Objectives Investigate the therapeutic response of refractory COVID or post-COVID headache to indomethacin.

Methods This was an observational, retrospective, open and uncontrolled. A sample of 37 patients diagnosed with COVID-19 presenting headache during the acute phase or after the resolution of the disease, with refractoriness to the usual symptomatic medication was treated with indomethacin.

Results Of the 37 patients (24 women and 13 men), 29 were migraineurs and 8 had no previous history of headache. The average age was 40.4 ± 9.4 years, ranging from 19 to 65 years. In 26 (70.3%) patients, the onset of headache occurred within 72 h, and in 11 (29.7%), after 10 days of positivity for Sars-CoV-2. After treatment with indomethacin, 36 patients reported greater than 50% headache relief from the third day and 5 became asymptomatic on the fifth day.

Conclusions In patients with migraine or no prior history of headache who present with refractory COVID or post-COVID headache to common analgesics, anti-inflammatory drugs, and/or triptans, indomethacin should be considered a therapeutic option.

Keywords Post-COVID headache · Refractory headache · Abortive treatment · Indomethacin

Introduction

Corona Virus Disease (COVID-19) is a disease caused by the newly identified human coronavirus (HCoV) named Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) [1, 2]. It has been a global pandemic since March 2020. Although it affects primarily the respiratory system, the loss of taste and smell, dizziness, encephalitis, encephalopathy, and cerebrovascular diseases are being frequently described as neurological symptoms or complications [1–3]. Headache, during the acute phase as well as manifesting as a post-infection symptom, has also been commonly reported [4, 5]. It affects 6.5–34% of COVID patients and may represent the only clinical manifestation [1–4]. Despite its high

prevalence, the management of this feature remains a challenge and little published evidence on the pharmacological treatment of COVID-19 headache is available. Non-steroidal anti-inflammatory drugs (NSAID) have been suggested, at least during the acute phase, but with anecdotal results [1, 2, 5, 6].

Indomethacin is a traditional NSAID with effective analgesic, antipyretic and anti-inflammatory activity [7]. It is an indole-acetic acid derivative available since the 1960s and probably one of the most potent compounds also derived from the acetic acid as diclofenac and sulindac. Not surprisingly, indomethacin was among the first NSAID used to treat headache in clinical practice including migraine and headache syndromes eventually known as “indomethacin-responsive” headaches [7].

In addition to the inhibition of cyclooxygenase, preventing the production of prostaglandins from arachidonic acid, indomethacin has a unique action that is not yet clarified. It may interfere with iontophoretically glutamate-activated dural-responsive second order neurons in the Trigeminal Nucleus Caudalis (TCC) [8]. Moreover, indomethacin may modulate

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nitric oxide (NO) signaling pathways. Nitric oxide is known to induce headache and delayed migraine in patients [9, 10]. In preclinical studies, indomethacin is able to inhibit NO-induced dural vasodilation [11], and this effect is unique because other NSAID also used for migraine such as naproxen or ibuprofen were ineffective in this regard [12].

COVID patients may have or not migraine as a comorbidity [1]. In addition, headache may occur during or after COVID with no clear relationship with migraine mechanisms [1, 13, 14]. However, some patients with migraine and COVID may seek help in general practitioners or emergency departments and receive unspecific prescriptions for the headache itself. Others will try using their usual acute migraine medications seeking to alleviate the head pain [13–16]. This retrospective study aimed at describing the outcomes of indomethacin use in patients, with or without migraine, who presented headache not responding to their acute medication during COVID acute phase or after > 10 days of confirmed infection by SARS-CoV-2.

Methods

Study design and participants

This was an observational, retrospective, open, uncontrolled, and descriptive study. The study population comprised a non-random and convenience sampling, consisting of consecutive patients with and without migraine seeking help at a tertiary headache center, to whom indomethacin was prescribed. Data for this study were collected from October 2020 to April 2021.

Inclusion and exclusion criteria

Patients over 18 years of age diagnosed with COVID-19, through the RT-PCR positivity for SARS-CoV-2 and presenting headache during the acute phase or after the resolution of the disease, with refractoriness to the usual symptomatic medication or to a symptomatic medication recently prescribed, for at least three days, were included in this study. The study excluded patients with acute headaches from secondary causes, such as acute glaucoma or acute sinusitis, and over the age of 60 years and pregnant women.

Data collection

Patients were divided into two groups: in group 1, those diagnosed with migraine without aura, according to ICHD-3 criteria [17], presenting less than 15 days of headache per month and in group 2, patients with no previous history of headache.

Indomethacin was prescribed at a dose of 50 mg, twice a day, orally, for 5 days, associated with pantoprazole 40 mg/day for all patients. Frequency and intensity of headache were assessed on the third and fifth days of treatment using a headache diary. We used a visual analog scale (VAS) to classify the intensity of pain as VAS 1–4 (mild), VAS 5–7 (moderate), VAS 8–9 (severe), and VAS 10 (very severe).

Ethical considerations

This study was approved by the Ethics in Research Involving Human Subjects Committee at the Federal University of Piauí, Brazil, protocol number 3.276.516 and the Presentation Certificate to Ethics Assessment, registry number 08973419.0.0000.5214, on August 22, 2020.

Statistical analysis

All collected data were organized in data base. The Statistical Package for Social Sciences (SPSS[®]) version 18.2.2 for statistical analysis was used. The quantitative variables were expressed as mean, standard deviation and minimum and maximum values, while qualitative variables were expressed as absolute and relative frequencies.

Results

A total of 37 patients (24 women and 13 men) were included in the study. The average age was 40.4 ± 9.4 years, ranging from 19 to 65 years (Table 1). Eight patients did not have a previous history of headache and were not patients of our center. They did seek help for the first time. The remaining 29 were migraineurs and had a severe headache for at least

Table 1 Distribution of sex and age of refractory COVID or post-COVID headache in 29 migraine patients and 8 without previous headache

Variables	Groups		<i>p</i> value
	Migraineurs <i>n</i> = 29	Without previous headache <i>n</i> = 8	
Sex			
Female (<i>n</i> ; %)	19 (65.5)	5 (62.5)	0.998 ^b
Male (<i>n</i> ; %)	10 (34.5)	3 (37.5)	
Age			
Average (SD)	40.8 (9.4)	38.9 (9.8)	0.615 ^a
Variation	19–65	29–56	

SD standard deviation, NA not applicable

^astudent's *t*-test *p* value for mean difference of unpaired samples

^b*p* value based on Fisher's exact test for mean difference of unpaired samples

three followed days during COVID-19 acute phase ($n = 21$) or started a daily headache for at least three followed days after a minimum of 10 days having tested positive for Sars-Cov-2 ($n = 8$). Both groups were not responding to their usual migraine symptomatic medication or to a medication prescribed by general practitioners specifically for the headache itself.

Migraine patients used preventive treatment with several options. Sixteen of them had daily headache of moderate to severe intensity within 2 days after a positive test for Coronavirus (5 with headache and mild airway symptoms and 11 with isolated headache). The other 13 migraine patients reported a headache that started after 10–16 days of testing positive for Coronavirus and they had, during the acute phase, mild or moderate respiratory symptoms. Four patients seek help at local hospitals during the acute phase.

Among the 8 patients without migraine, 5 (62.5%) had a severe headache during the acute phase and 3 after 10–13 days thereafter. All of them received metamizole and / or NSAID other than indomethacin. Three patients also received oral prednisone and five patients went to local hospitals for receiving care.

Indomethacin was prescribed for all patients. Thirty-six patients reported greater than 50% headache relief from the third day and 5 became asymptomatic on the fifth day. One patient, a 36-year-old female with a previous history of migraine did not refer any improvement. She was later diagnosed with pachymeningitis and treated with steroids.

All 37 patients had a normal neurological examination, and none had abnormal oxygen saturation, fever, or any other physical abnormality. However, nearly half referred moderate or severe asthenia. All patients who seek help in local hospitals had their D-dimer measured and none presented abnormalities.

The distribution of the clinical characteristics of refractory COVID or post-COVID headache in 29 migraine patients and 8 without previous headache is summarized in Tables 2, 3.

Discussion

COVID-19 or post-COVID-19 headache is a bothersome symptom and may be the only COVID-19 symptom [1, 6]. However, headache is also a symptom commonly reported in various viral infections such as dengue and chikungunya that are common in the tropical regions and therefore may not be specific for COVID-19 [18, 19]. Although the headache prevalence in COVID varies with different geographic regions, it may occur in higher than one third of the patients [2, 4, 6].

The true prevalence of headache in COVID patients is uncertain. In a review of 78 studies consisting of 104,751

Table 2 Clinical characteristics of refractory COVID or post-COVID headache and therapeutic response to indomethacin in 29 migraine patients and 8 without previous headache

Characteristics	Groups				<i>p</i> value
	Migraineurs		Without previous headache		
	<i>n</i>	%	<i>n</i>	%	
Headache onset					
Within 72 h	21	72.4	5	62.5	0.672
After 10 days	8	27.6	3	37.5	
Improvement over 50% with 3 days					
Yes	28	95.6	8	100.0	1.000
No	1	3.4	0	0.0	
Asymptomatic with 5 days					
Yes	20	69.0	6	75.0	1.000
No	9	31.0	2	25.0	
They received hospital care					
Yes	4	13.8	5	62.5	0.011
No	25	86.2	3	37.5	

p values were calculated using Fisher's exact test

COVID-19 patients, headache was reported in 26,464 patients with a cumulative prevalence of 25.26% [20].

The headache location is also varied. Up to 2% of sufferers had a temporal headache, while 35.3% complained of frontal and 23.5% had retro-orbital headache. Up to 39.2% reported diffuse headache [21]. The quality of the headache may also be differently reported by the patients. In a study, which involved 46 patients, 86% had tension-type pain and 14% had migraine-like headache [22]. It was not clear whether patients had a previous history of headache attacks. In addition, not all patients refer severe headache [23, 24].

No clear mechanisms have been reported on how these headaches emerge in COVID-19 patients [25, 26]. However, it has been proposed that the activation of trigeminal nerve ending in the periphery followed by the sensitization of various sites in the brain is one of the main pathophysiological features of headache in these patients [25, 26].

The treatment of headache in COVID-19 patients may be difficult [6]. There is no consensus on drugs for this specific type of headache and numerous drugs have been tried with anecdotal results [6]. In a case report, a chronic migraine patient already in use of fremanezumab with comorbidities COVID-19, had a refractory headache. After the use of numerous drugs, she received lacosamide IV and other pharmacological agents with supposed amelioration [27]. Non-steroidal anti-inflammatory drugs were initially contraindicated for COVID-19 patients by the World Health Organization (WHO), but soon after the contraindication was retracted [28].

Table 3 Clinical characteristics of refractory COVID or post-COVID headache in 29 migraine patients infected with Sars-CoV-2

Variables		
Age of onset of pain (years)		
Average (SD)		21.1 (10.5)
Variation		8–50
Headache characteristics (<i>n</i> ; %)		
Intense daily headache within 2 days (5 with headache and mild airway symptoms and 11 with isolated headache)	16	55.2
Headache that started after 10–16 days	13	44.8
Prophylactic medications (<i>n</i> ; %)		
Candesartan	1	3.5
Divalproate	7	24.1
Divalproate and atenolol	2	6.9
Divalproate and candesartan	4	13.8
Nortriptyline, flunarizine and tizanidine	10	34.5
Topiramate and nortriptyline	5	17.2

Although with retrospective and open design, our study suggests that indomethacin may be useful for these patients. Indomethacin was already suggested as a useful treatment not only for COVID-19 headache, but, in addition, for COVID-19 induced dry cough [29].

Moreover, the contagion of COVID-19 leads to a burst release of the cytokines that may increase the severity of the infection mainly due to heightened immunopathogenicity. The pro-inflammatory metabolites, COX-2, cPLA2, and 5-LOX enzymes involved in their generation, and the substrates that instigate the origination of the innate inflammatory response therefore play an important role in intensifying and worsening of the tissue morbidity related to the coronavirus infection. Drugs with potential for inhibiting these overexpressed immunogenic pathways in the tissues invaded by coronaviruses has been a matter of debate since the inception of the pandemic. The effectiveness of NSAIDs such as Indomethacin in COVID-19 coagulopathy, discouraging the SARS viral replication, the inflammasome deactivation, and synergistic inhibition of H5N1 viral infection with representative antiviral drugs, have provided a silver lining in adjuvant COVID-19 therapy [30, 31].

In addition, indomethacin exerts its anti-inflammatory actions though the inhibition of TNF, IL-6 and superoxide free radicals besides the inhibition of COX-1 and-2. Since it also inhibits viral protein synthesis and has been studied against herpes virus 6, cytomegalovirus and hepatitis B virus, a possible action against SARS-Cov-2 has been considered. In vitro and in vivo studies, indomethacin reduced viral RNA synthesis in SARS-Cov of monkey vero cells and in canine infections [32].

The main reason why we chose indomethacin to these patients was the lack of efficacy referred by all when treating their headache with metamizole (usually

prescribed in Brazil for COVID-19 patient with headache), paracetamol, other NSAID and triptans, which were used by the patients with comorbid migraine. Additionally, indomethacin is an inexpensive and readily available drug with demonstrated efficacy in numerous headache syndromes [7].

The use of 5-day cycle of indomethacin 50 mg BID may have ended the headache or was only a coincidence. We cannot assure that indomethacin was the responsible for alleviating the headache, which could have been demonstrated with a placebo-controlled study.

Conclusions

In patients with migraine or no prior history of headache who present with refractory COVID or post-COVID headache to common analgesics, anti-inflammatory drugs, and/or triptans, indomethacin should be considered a therapeutic option.

Funding This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Declarations

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

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all participants.

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