



## ORIGINAL ARTICLE

## Usage of Phenytoin in Treatment of severe Headache in COVID-19 Patients

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### KEYWORDS

Phenytoin;  
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**ABSTRACT:** COVID-19 is a viral infection transmitted through the respiratory system, caused by Coronavirus type 2 usually get excess to the body through Flügge microdroplet of an infected person to a healthy one with air although direct contact and aerosol may be another route for transmission. This is a prospective study of 500 patients (63% women) conducted in a medical city in Baghdad. In a study patients' collection started in Aug 2020 for six weeks. They followed for at least six months after they recovered from COVID-19. Among 500 patients included 53.4% were male (out of those 118 were complain of severe headaches 23.6%), while females comprise about 46.6% of total patients of that 13% had severe headaches. The highest age group with severe headaches was (60-65) years coming next (51-55) years. group A had a partial response to drugs used although more than 60% respond to a combination of Ibuprofen and Acetaminophen, while in group B good control of Headache was achieved (80%) when adding Phenytoin to treatment protocol during and after the acute stage of the disease. There is controversy about the treatment of headaches caused by COVID-19 but for sure, Acetomenaphin combined with NSADI drugs is the best and safe choice. In refractory cases, antiepileptic drugs like phenytoin are added to achieve freedom of pain and for a long-term period.

### INTRODUCTION

COVID-19 is a viral infection transmitted through the respiratory system, caused by Coronavirus type 2 usually get excess to the body through Flügge microdroplet of an infected person to a healthy one with air although direct contact and aerosol may be another route for transmission [1]. Headache in combination with other symptoms of influenza-like nasal congestion, fatigue, myalgia, anosmia, sore throat, and other known features are recognized but variable severity in patients with COVID-19. Unfortunately, patients may be complicated from the start

by respiratory distress syndrome, pneumonia, and sepsis. Headache was the fifth in the list of the most common symptoms and presented in about 20-55% of total patients with COVID-19 [1, 2]. During active disease, headache may continue for a few days while in others it can last longer (up to a few months) during the follow-up period [3]. The origin of headache in such patients can be attributed to the systemic viral infection itself, tension headache, cough-induced headache, heterophobia in the first phase of the infection, hypoxia-induced, and finally,

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headache in the second phase occurs (cytokine storm) [1,2]. Most of the patient's headaches are caused by the virus through the binding with the trigeminal nerve endings in the nasal cavity (ACE2) resulting in trigeminovascular stimulation. This is also may be the cause of loss of smell and taste sense. The severity of this symptom depends on the viral load in the nasal cavity in addition to the presence of active infection near cranial nerves in this site in combination with the inflammatory response. Usually, headache mainly occurs in young patients compared to the older one and almost citing short course of the disease compared to those without headaches [4]. In this respect, the exact pathology of headache in COVID-19 is not yet determined and the virus itself due to psychological factors,

using many chemical protective materials, may indirectly cause it or the occurrence of the headache at the same time as the development of viral infection symptoms may attribute the virus as the direct cause [2]. Headaches are regarded as mild if the patients can carry on their daily life activity in the usual way while those with a reduction in their daily activity are regarded as moderate on the other hand patients who stopped their daily activity due to headaches are considered to be severe [5]. Some Authors use a pain scale for assessment of the severity of pain where the pain severity is divided into 10 degrees [6]. Figure 1 describes the numerical grading of headache severity.

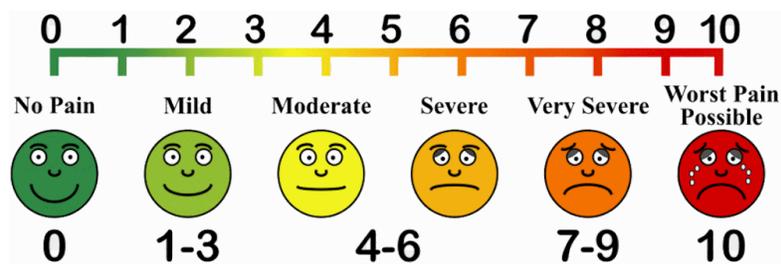


Figure 1. Describe numerical grading of headache severity.

There are controversies about treatment options for headaches in COVID-19 patients some authors use acetaminophens alone or in combination with nonsteroidal anti-inflammatory (NSID) drugs while others use Migraine drugs [7]. This study was performed aimed to assess the effects of Phenytoin drug in the treatment of severe headaches in patients with COVID-19 infection.

## MATERIALS AND METHODS

This is a prospective study of 500 patients (63% women) conducted in a medical city in Baghdad. The limitation of this study is that this viral infection attacked human beings recently not many articles and studies have been published about the treatment of its symptoms, especially severe ones. In a study patients' collection started in Aug 2020 for six weeks. They followed for at least six months after they recovered from COVID-19. Patients included in this study how could give consent and undergo a full interview, diagnosed to have moderate to severe acute respiratory Coronavirus (COVID-19) infection, presented with

multiple symptoms (Based on the symptoms recorded by the world health organization [8]. In which Headache presented as the main or one of the presenting symptoms. Headaches are regarded as mild if the patients can carry on their daily life activity in the usual way while those with a reduction in their daily activity are regarded as moderate on the other hand patients who stopped their daily activity due to headaches are considered to be severe [5]. Patients with moderate to severe headaches were included in this study. All patients are diagnosed depending on clinical assessment in addition to positive serological test and/or radiological computed tomography/X-ray of the lung. Those proved to have positive COVID-19, assessed by routine investigations including C-reactive protein as an inflammatory marker (positive above 0.5 mg dl); Serum Ferritin (normally 25-250 ng ml), Lactate Dehydrogenase (LDH: 0-248 UI L); and D-dimer: (0-243 ng mL). Those patients do not have any serological or radiological evidence excluded. In addition, patients with mild-moderate headaches were excluded together with those that did not follow regular assessments after they had been free

of infection. Patients free of respiratory or other serious organs involvement supported by normal vital signs, physical examination, and radiological CT scan or X-ray were not admitted to the hospital and followed at home. After confirmation of headache as symptoms attributed to COVID-19, we gave Acetaminophen (500mg-3g day) with Ibuprofen (200mg-1200mg day) orally to half of the patients as a part of their treatment regimen for relieving fever and other symptoms (group A) during the acute attacks and then one of them after the patients clear of the infection while another half (Group B) we use one of these drugs or both with Phenytoin orally just as a treatment option for headache in a dose 100-300 mg according to the severity and the response of the patients with a regular check for renal and liver functions. Many papers recently support that Phenytoin has good effects in trigeminal neuralgia and as a painkiller [9].

**RESULTS**

In this study, 500 patients included 53.4% were male, (out of those 118 were complain of severe headache 23.6%), while females comprise about 46.6% of total patients of

that 13% had a severe headache. Table 1: The mean age of the patients was years. The highest age group with severe headaches was (60-65) years coming next (51-55) years. Total patients with severe headaches were 183 (36.6%), although others may have mild to moderate they are not included in this study.

The clinical features are shown in Table 2.

Regarding the response to treatment, group A had a partial response to drugs used although more than 60% respond to a combination of Ibuprofen and Acetaminophen, while in group B good control of Headache was achieved (80%) when adding Phenytoin to treatment protocol during and after the acute stage of the disease. As shown in Table 3, Both groups showed good response to treatment used on long term follow up although Group B record better response although with the long term follow up fewer patients complain from headache and need more treatments. No significant side effects have been recorded from the use of Phenytoin in this short period of treatment, as shown in Table 4.

Also, Table 5 presents the patient's need for treatment for headaches after the infection subside.

**Table 1.** Demographic distribution of Age and gender.

	Total patients (n=500)		Patients with severe Headache	
<b>Male</b>	267	53.4%	118	23.6%
<b>female</b>	233	46.6%	65	13%
<b>AGE</b>				
<b>20-25Years</b>	33	6.6%	12	6.6%
<b>26-30Years</b>	15	3%	5	2.75%
<b>31-35Years</b>	23	4.6%	7	3.85%
<b>36-40Years</b>	31	6.2%	17	9.35%
<b>41-45Years</b>	45	9%	23	12.65%
<b>46-50Years</b>	55	11%	15	8.25%
<b>51-55Years</b>	44	8.8%	26	14.3%
<b>56-60Years</b>	61	12.2%	13	7.15%
<b>61-65Years</b>	67	13.4%	34	18.7%
<b>66-70Years</b>	52	10.4%	14	7.7%
<b>71-75Years</b>	74	14.8%	17	9.35%
<b>Total</b>	500	100%	183	

**Table 2.** Clinical features.

Presentations	Group A n=91	Group B n=92
Severe Headache	91	92
Fever	44	53
Malaise	50	65
Myalgia	35	52
Dizziness	20	20
Cough	27	37
Dyspnea	13	21
Chest pain	10	18
Loss of sense taste/smell	75	80
Diarrhea	19	10

**Table 3.** Response of patients to treatments.

Headache severity post-treatment	0 pain scale	1 pain scale	2 pain scale	3 pain scale	4 pain scale	5 pain scale	6 pain scale	7 pain scale	8 pain scale	9 pain scale	10 pain scale
Group A n= 46	--	--	--	--	--	--	8 17.36%	9 19.53%	15 32.55%	9 19.53%	5 10.85%
Group B n=45	--	--	--	--	--	--	6 13.32%	8 17.76%	11 24.42%	13 28.86%	7 15.54%
Group C n= 92	--	--	--	--	--	--	15 16.2%	22 23.76%	30 32.4%	14 15.2%	11 11.88%

**Table 4.** Patients need treatment of headache after infection subsides.

Headache severity post-treatment	0 pain scale	1 pain scale	2 pain scale	3 pain scale	4 pain scale	5 pain scale	6 pain scale	7 pain scale	8 pain scale	9 pain scale	10pain scale
Group A n= 46	5 10.5%	1 2.1%	8 16.8%	7 14.7%	4 8.4%	9 18.9%	--	5 10.5%	2 4.2%	5 10.5%	--
Group B n=45	--	8 17.76%	3 6.66%	15 33.3 %	7 15.54 %	--	--	7 15.54%	5 11.1%	--	--
Group C n= 92	26 28.08%	14 15.12%	29 31.32%	13 14.04%	6 6.48%	--	2 2.16%	2 2.16%	--	--	--

**Table 5.** Patients need treatment of headache after infection subsides.

Pat. Need treatment	Group A	percentage	Group B	percentage	Group C	percentage
After 4weeks	26	56.42%	21	46.62%	23	24.84%
After 8weeks	17	36.89%	17	37.74%	13	14.04%
After 12weeks	13	28.21%	10	22.2%	7	7.56%
After 24weeks	10	21.7%	6	13.32%	2	2.16%

## DISCUSSION

COVID-19 global crisis that threatens human beings' health, it expressed in many features that may differ from one patient to another which made dealing with such disease a challenge for many specialties including neurologists. According to results obtained, no association has been found between the development of headache or its severity with the gender and the age of the patients, this is also true regarding other clinical features that the patients complain about as a result of the infection with COVID-19. This study discusses the treatment of severe headaches that interferes with the daily activity of the patients through the use of a combination of drug (Ibuprofen and Acetaminophen) in one group while in another group we add to them another drug (Phenytoin) depending on the fact that this drug used as a pain killer and in treatment of trigeminal neuralgia were most of the headache in COVID-19 patients are attributed to the trigeminovascular stimulation in addition to its antiepileptic effect [4,9]. We notice that the group A patients get a response to the usual treatment used by many physicians but when compared to group B we noticed that good results were achieved by adding Phenytoin to their treatment protocol in which more patients are free of pain during the acute stage and even for a long period after the infection has been subsiding as some patients may have headache weeks later [4]. Karissa N. et, al. used NSAID together with corticosteroids, and they found that there is a risk of using corticosteroids unless mandatory in some patients like asthmatics [10]. While in other literature Karissa used anticonvulsants as a treatment option with the least risk for the patients [11]. Morollón concludes that any type of standard treatment for headache and neuralgia can be used without contraindication [12]. DIMOS Conclude that NSAID good choice as a treatment for headaches which the FDA agrees with such advice, and also advice for the use of paracetamol and triptans in Migraine attacks [13]. There is no convincing evidence that either RAS blockers or ibuprofen facilitate or worsen

SARS-CoV-2 infection in any type of patient, including headache patients, there is no convincing evidence that either RAS blockers or ibuprofen facilitate or worsen SARS-CoV-2 infection in any type of patient, including headache patients, there is no convincing evidence that either RAS blockers or ibuprofen facilitate or worsen SARS-CoV-2 infection in any type of patient, including headache patients. Antoinette found that COVID-19 are not worsened or facilitated by Ibuprofen in any patients complaining of headache due to this virus [14]. Osman found that the occurrence of headaches during the COVID-19 course may indicate the shorter course of the disease and may suffer headache persistence for several weeks [4]. That is why we use treatments for some patients for up to six months.

## CONCLUSIONS

There is controversy about the treatment of headaches caused by COVID-19 but for sure, Acetomenaphin combined with NSADI drugs is the best and safe choice. In refractory cases, antiepileptic drugs like phenytoin are added to achieve freedom of pain and for a long-term period.

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### *Conflict of interest*

The authors declare that there is no conflict of interests regarding the publication of this paper.

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