

## COMPARISON OF STEROIDS TO NSAIDS, AND OTHER FORMS OF ANALGESIA IN THE MANAGEMENT OF POST-CHIKUNGUNYA ARTHRITIS

Hamza Alam, Tahira Perveen Umer, Iffat Khanum, Lubna Nazir, Uzma Erum, Muhammad Irfan

Liaquat National Hospital and Medical College, Karachi Pakistan

### ABSTRACT

**Objective:** To compare steroids with other treatment options like NSAIDs and other analgesics for management of post-chikungunya arthritis based on visual analogue scale (VAS).

**Study Design:** Comparative cross-sectional study.

**Place and Duration of Study:** Department of Rheumatology, Liaquat National Hospital, Karachi, from Jan to Jul 2018.

**Methodology:** A total of 112 patients were included in this study, of both genders. Patients with history of fever  $>38.5^{\circ}\text{C}$  and polyarthralgia who had positive chikungunya IgM serology or PCR were included in this study. Patients fulfilling inclusion criteria and who were treatment naïve were given NSAIDs or other analgesics if contraindication to NSAIDs was present. Those who had received 2 weeks of NSAIDs were given a single dose of intramuscular steroids. Response to treatment was characterized by clinical examination according to visual analogue scale (VAS) taken at baseline, 2 weeks and 4 weeks. All analyses will be conducted by using SPSS-20.

**Results:** Overall, 66 (58.9%) received steroids, 37 (33%) patients were given NSAIDs, and other forms of analgesics were prescribed to 9 (8%) patients. In nearly half of the patients, i.e. 57 (50.89%) partial response was seen, 13 (11.6%) showed complete response, while 42 (37.5%) had persistent arthralgia, which was statistically significant  $p$ -value  $<0.001$ .

**Conclusion:** This study shows that improvement in symptoms is seen with a single dose of intra-muscular steroid and it helped bring down the VAS score.

**Keywords:** Chikungunya viral fever, Post-chikungunya arthritis, Post-infectious arthritis.

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### INTRODUCTION

Chikungunya virus (CHIKV) belongs to the Togaviridae family<sup>1</sup>. It derives its name from Makonde language which means “that which bends up”. This refers to the posture of patients afflicted with severe joint pain which characterizes this infection<sup>2</sup>. There were 1,675,387 cases reported across different regions of the world from December 2013 to September 2015<sup>3</sup>.

The commonest vector for CHIKV transmission to humans is Aedes mosquito. The symptoms generally commence 4-7 days after the mosquito bite. Generally acute infection lasts for 1-10 days. After that it is characterized by abrupt onset of fever, fatigue, headache, vomiting, nausea, myalgia, rash, and severe arthralgia.

Painful polyarthralgia is the symptom causing serious socio-economic impacts on the individuals and the affected communities as well<sup>4</sup>.

CHIKV infection can be diagnosed by the presence of virus's RNA in serum of patient by a polymerase chain reaction (PCR) method. However, anti-chikungunya IgM antibody may be detected in the blood for 6 months or longer and is diagnostic of a

recent infection<sup>5</sup>.

Unfortunately, due to improper sanitation and poor hygienic condition, the propagation of vectors for causing malaria, dengue, CHIKV and other infectious diseases has been continuous. Pakistan's first case of CHIKV infection was detected in Karachi in December 2016, and the numbers are increasing since then. However, no mortality has been reported so far.

The chronic persistent arthritis in association with CHIKV may span over couple of months and it has a negative impact on everyday activities. Hence, it is prudent to carefully look for the clinical and laboratory features which have been associated with persistent arthralgia in CHIKV patients. This study was designed to point out the factors that could lead to the persistence of severe joint pains and adverse outcome in patients with chikungunya arthritis. It will also help clinicians in better comprehension of the disease itself and differentiating it from other conditions that mimic CHIKV associated arthralgia or vice versa. There are very few studies pertaining to the CHIKV epidemic which hit Karachi.

### METHODOLOGY

This was a comparative cross sectional study conducted in the department of rheumatology, Liaquat National Hospital, from January 2018 to July 2018. The

**Correspondence:** Dr Humza Alam, D-140, Block 7, Gulshan-e-Iqbal, Karachi Pakistan

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sample size was calculated using the WHO sample size calculator considering  $P=38\%$ ,  $d=9\%$  and 95% confidence interval, it was 112 patients. Sampling technique used was non-probability, consecutive sampling. All patients, both male and female, who presented to the rheumatology clinic with history of fever  $>38.5^{\circ}\text{C}$  and acute onset polyarthralgia, and had a positive chikungunya serology, both IgM and IgG, were incorporated into this study. Patients with underlying rheumatic diseases presenting with sudden flare in symptoms and having a positive chikungunya serology were also included in the study. Co-infection with dengue virus and other acute febrile illnesses like enteric fever, malaria were excluded from this study.

Patients who were treatment naïve were started on NSAIDs, if no response was seen in 2 weeks, or patients who had taken prior NSAIDs for 2 weeks or more were given a single dose of intramuscular methylprednisolone 120 mg. All patients were assessed at 0, 2 and 4 weeks. Treatment response was assessed according to visual analogue scale (VAS). Patients were divided into groups based on the VAS score at the 4th week. Partial response was defined as having a VAS score between 1 to 5, complete response was defined as having a score of 0, while persistent arthralgia was defined as VAS score of more than 5.

All patients who fulfilled the inclusion criteria were considered for the study. Ethical committee permission was taken. Its approval certificate number was app # 0421-2018-LNH-ERC. Complete history and examination was done for every patient. Age, sex, fever duration, quantity of joints involved, as well as any co-morbidities were noted. Complete blood count (CBC), c-reactive protein (CRP), erythrocyte sedimentation rate (ESR), chikungunya serology IgM; IgG were done. All patients also underwent anti-nuclear antibody (ANA) and anti-cyclic citrullinated peptide (anti-CCP) testing to rule out other autoimmune diseases that might mimic post-chikungunya arthritis. A pre-designed proforma was made for data collection. Patient's confidentiality was properly maintained and consent was taken. Data was analysed by SPSS-20. Calculation of mean and standard deviation was performed for quantitative variables. Frequency and percentage were calculated for categorical variables. mean comparison was done by independent t-test. Stratification was done according to age, sex, fever duration, number of joints, symptom duration and laboratory parameters. Post stratification Chi square test and

Fisher exact test was applied as appropriate by taking  $p\text{-value} \leq 0.05$  as significant.

## RESULTS

A total of 112 patients were included in the study. Out of which 82 (73.2%) belonged to female gender, and 30 (26.8%) to male. The mean age was  $48 \pm 12$  years. Mean duration of fever was  $10.92 \pm 17.33$  days, while mean duration of arthritis was  $2.6 \pm 1.8$  months. Patient's presentation, with regard to joint symptoms, was varied in time; 28 (25%) patients presented in the first month of illness; 42 (37.5%) in the second month, and 16 (14.3%) patients presented in third month. Only 2 (1.8%) patients presented to us after 6 months of onset of symptoms. Associated co-morbidities like diabetes mellitus (18.7%), hypertension (52.5%), ischemic heart disease (7.1%), chronic kidney disease (6.2%) were seen. Among all, 5 (4.4%) patients had a pre-existing rheumatologic disorder.

**Table-I: Characteristics of study population.**

	Mean $\pm$ SD
Age (years)	47.91 $\pm$ 12.76
Hemoglobin (g/dl)	12.32 $\pm$ 1.63
Total leukocyte count ( $\times 10^9/\text{L}$ )	7.34 $\pm$ 2.46
Neutrophils (%)	59.85 $\pm$ 6.35
Lymphocytes (%)	32.64 $\pm$ 4.72
Eosinophils (%)	2.41 $\pm$ 0.83
Platelets ( $\times 10^9/\text{L}$ )	289.84 $\pm$ 91.28
	<b>n (%)</b>
<b>ESR</b>	
Normal	31 (27.6)
Increased	81 (72.4)
<b>CRP</b>	
Normal	42 (37.5)
Increased	70 (62.5)
<b>Treatment</b>	
NSAIDs	37 (33)
Steroids	66 (58.9)
Other forms of Analgesia	9 (8)
<b>Outcome</b>	
VAS at baseline	8.48 $\pm$ 1.13
VAS at 2 weeks	6.24 $\pm$ 1.9
VAS at 4 weeks	3.39 $\pm$ 0.95

With regard to joint involvement 85 (75.9%) and 27 (24.1%) had symmetrical and asymmetrical involvement respectively. Types of joint are small, medium and large Joint involvement in 78 (69.6%), while only large joint involvement was seen in 34 (30.4%) patients. Morning stiffness of half hour or more was seen in 74 (66.1%) patients.

With regard to treatment NSAIDS were given to 37 (33%) patients, while steroids to 66 (58.9%), and 9 (8%) received other forms of analgesics. Overall, 57 (50.89%) showed partial response, complete response was seen in 13 (11.6%), while persistent arthralgia in 42

Positive CHIKV IgM was seen in 86 (76.2%) patients, while IgG was seen in 88 (78.6%) patients (fig-1). The mean duration of presentation to us with arthritis was  $2.09 \pm 1.69$  and  $2.99 \pm 1.95$  months, for IgM and IgG respectively.

**Table-II: Association and mean comparison of treatment with outcome.**

Treatment	n (%)			p-value
	Partial Response (n=57)	Complete Response (n=13)	Persistent Arthralgia (n=42)	
NSAIDS	4 (7.0)	-	33 (78.5)	<0.001
Steroids	48 (84.2)	13 (100)	5 (11.9)	
Other forms of Analgesia	5 (8.7)	-	4 (10.8)	

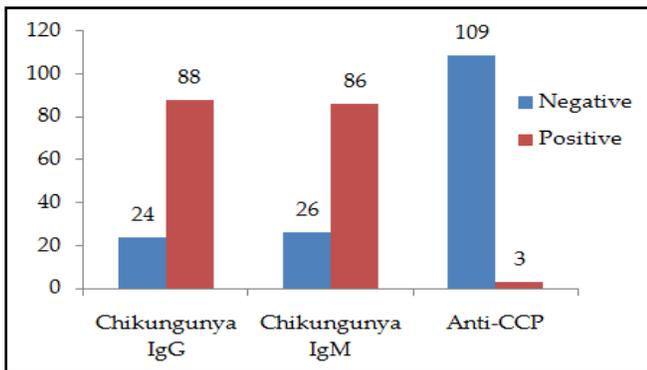
p-value ≤0.05, considered as significant.

**Table-III: Association and mean comparison of IgM and IgG.**

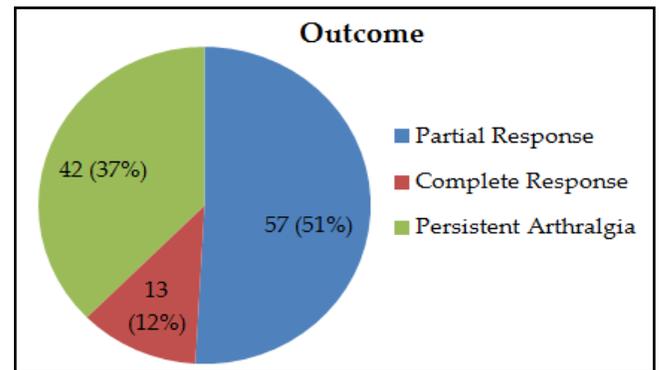
	IgM n(%)		p-value	IgG n(%)		p-value
	Positive (n=86)	Negative (n=26)		Positive (n=88)	Negative (n=24)	
<b>Fever Duration</b>						
≤7 days	53 (61.6)	24 (92.3)	0.003	72 (81.8)	7 (29.2)	<0.001
>7 days	33 (38.4)	2 (7.7)		16 (18.2)	17 (70.8)	
Arthralgia Duration (months)	$2.09 \pm 1.69$	$4.38 \pm 0.85$	<0.001	$2.99 \pm 1.95$	$1.59 \pm 0.62$	<0.001
<b>Arthralgia Duration Group</b>						
≤6 Months	84 (97.7)	26 (100)	1.000	86 (97.7)	24 (100)	1.000
>6 months	2 (2.3)	-		2 (2.3)	-	

(37.5%) patients. At baseline mean VAS score was  $8.48 \pm 1.13$ , at 2 weeks it was  $6.24 \pm 1.9$  and at 4 weeks it was  $3.39 \pm 0.95$  (table-I). Out of 66 patients who received steroids, partial response was seen in 48 (84.2%), 13 (19.7%) showed complete response, while persistent arthralgia in 5 (11.9%) patients ( $p=0.000$ ) (table-II & fig-2). Only 12 (9.6%) patients were hospitalized second-

Persistent arthralgia was reported in 5 patients and were treated with steroids. Of these 5 patients, 3 remained to have recurrent synovitis and later developed positive anti-CCP antibodies, hence rheumatoid arthritis. The other two patients also had recurrent joint symptoms, which were refractory to steroids. However, they remained negative for anti-CCP anti-



**Figure-1: Positive serologies associated with post-chikungunya arthritis.**



**Figure-2: Response to treatment seen in total number of patients afflicted with Post-chikungunya arthritis.**

ary to complications like severity of joint pain, encephalitis and septic arthritis ( $p=0.002$ ).

bodies, but were treated with methotrexate and hydroxychloroquine. All these 5 patients had high titres of CHIKV IgM at 6 months.

## DISCUSSION

Post infectious arthritis has been challenging for rheumatologists for many decades. Management of post infectious joint pain is a challenge, especially in third world countries where infections are rampant. Most post infectious arthritis manifest as reactive arthritis which is usually oligoarticular and has an underlying autoimmune etiology<sup>6</sup>. However, arthritis and arthralgia accompanying chikungunya has resembled polyarticular inflammatory arthritis to a large extent<sup>7</sup>. Often it has been difficult to distinguish between these two.

In general, it has been reported that chikungunya fever affects both genders equally, though in the context of post viral arthralgia females are predominantly affected. A study by Borgherini *et al.* reported a male to female patient's ratio of 1.24:1<sup>8</sup>. It has been reported that 36 months after acute infection, 60% of CHIKV-infected patients suffered from arthralgia. In addition, majority of patients had relapsing arthralgia, while approximately 40% had unremitting arthralgia<sup>9</sup>. Another study conducted by Borgherini *et al* reported persistent polyarthralgia related to CHIKV infection, and in 63.6% patients<sup>10</sup>. Apart from this pattern of joint involvement was symmetrical polyarticular, and morning stiffness were typically seen in patients with post-chikungunya arthritis and often led us to think whether it has triggered an underlying autoimmune process which has led to severe polyarthritis. Thus, chronic chikungunya arthritis needs to be differentiated from inflammatory arthritis<sup>11</sup>.

Laboratory parameters especially raised acute phase reactants, with more than adequate response to steroids, also made it difficult to differentiate it from an inflammatory arthritis.

The optimal treatment for CHIKV and associated arthritis remains an unanswered challenge for physicians worldwide<sup>12</sup>. As there is lack of licensed vaccines or effective medications available against CHIKV, most of the treatment regimens available are symptomatic. Non-steroidal anti-inflammatory drugs (NSAIDs) and non-salicylate analgesics are most commonly used for symptomatic relief, as methotrexate and TNF inhibitor for chronic cases<sup>13,14</sup>. To date no specific treatment with antiviral has been proven to treat CHIKV<sup>15</sup>. In this study patients who were treatment naïve were started on NSAIDs, if no response was seen in 2 weeks, or patients who had taken prior NSAIDs for 2 weeks or more were given a single dose of intramuscular methylprednisolone 120 mg<sup>16</sup>. If no response was seen over

a month then these patients were labeled as having persistent arthritis and were given low dose oral prednisolone and methotrexate (MTX). Patients showing improvement in symptoms and complete response were further followed up at 6 months to assess for recurrence of symptoms. In a study of Chang *et al* of 500 patients it was found out that women were more likely to have chikungunya virus infection symptoms as was the same in our study. Pattern of joint was also same showing predominant symmetrical small to medium joint involvement, with early morning stiffness. However, study by Chang *et al* divided treatment into groups taking either acetaminophen, ibuprofen, prednisolone, methotrexate, aspirin, etc. Patients taking acetaminophen and ibuprofen were more in number and response rate was poor, the same in our study. It is difficult to comment on patients taking steroid as their numbers were very small<sup>22</sup>.

Treatment with other forms of analgesia like paracetamol and narcotics was mostly due to relative contraindications or intolerance to the aforementioned drugs. In this study visual analogue scale (VAS) was used to assess response to treatment. VAS score improvement was seen on subsequent follow up at 2 and 4 weeks. Patient treated with steroids showed improved VAS scores compared to patients who were given NSAIDs. Over 58.9% of our patients received a single dose of intramuscular methylprednisolone. Of them partial response (VAS score <5) was seen in 72.7%, while complete response (VAS score 0) in 19.7%. This was seen as an easy and cost effective option in alleviating symptoms. A study by Sharma *et al* of 99 patients showed symmetrical polyarthritis in 93.9% of patients as compared to 75.9% seen in our study. In the fore mentioned study patients were divided into 3 treatment groups namely NSAIDs, NSAIDs + steroids, and NSAIDs + steroids + MTX which had varying response rates of 73.6%, 63.6% and 83.3% respectively. However, our study showed marked improvement in the steroid alone group 58.9% while mild improvement in the NSAIDs alone group 33%<sup>21</sup>.

A study by Amaral *et al* showed that chronic arthritis of chikungunya may develop joint deformities and depression similar to rheumatoid arthritis, fibro-myalgia and other rheumatic diseases. It also reported a considerable response with MTX usage in these patients<sup>17</sup>. Apart from this hydroxychloroquine, sulfa-salazine, methotrexate and biological agents can be used<sup>18</sup>. Whether or not this strategy would help in prompt recovery and halting of disease process in these patients

is too early to predict. Larger studies are required to evaluate the efficacy of these advanced treatment options for patients with CHIKV associated arthritis. In addition, there is a need of definite treatment guideline regarding management of arthritis accompanying CHIKV.

Other important thing to note is the predisposition of rheumatoid arthritis. Most of these patients had persistent symptoms and active synovitis, even months after CHIKV. They were found to be anti-CCP positive later in the disease course<sup>19</sup>. Despite the fact that their initial work-up for RA was negative. In addition, all of them were found to have persistently high titers of IgM serology. This has risen the possibility of chikungunya viral infection being a potential trigger for development of rheumatoid arthritis. Nonetheless, these predisposing factors remain to be elucidated.

At the very moment, there is no evidence of a definitive causal link between initial viral infection caused by CHIKV and development of chronic inflammatory joint disease or the inciting factors for triggering of an autoimmune mechanism. Additional, prospective clinical research and trials are required to further determine the potential role of CHIKV antibodies and development of chronic joint disease<sup>20</sup>.

Though this is a small cohort of patients but it points towards the notion that post-chikungunya viral arthritis has emerged as a major debilitating disease and has posed a significant socioeconomic burden with close mimicking features of rheumatoid arthritis. This study helped us in concluding that a single dose of methylprednisolone was helpful in managing patients successfully who experienced post-chikungunya arthritis and also this did not have a significant impact on patients monetary wise. With all this said further research needs to be conducted on establishing the link between chikungunya virus and it triggering inflammatory arthritis. This study had a few limitations given the vast population which was afflicted by CHIKV our sample size was small, and further long term follow up is required to monitor these patients.

## CONCLUSION

This study represents a close resemblance between rheumatoid arthritis and post-inflammatory viral arthritis. A single shot of methylprednisolone is an effective treatment modality for symptomatic relief. Nonetheless, all the patients with CHIKV should thoroughly be evaluated clinically and with serological markers, both initially and in long term follow-up.

## Disclosure

Article presented as a poster in ACR, EULAR annual meeting in 2018.

## CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any authors.

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