ORIGINAL ARTICLE

JIACM 2018; 19(2): 102-05

A Comparitive Study of Short Course Corticosteroids v/s NSAIDS in Debilitating Post-Chikungunya Arthritis

Shweta Sharma, Dhanveer Singh**, Abha Gupta***, Prakhar Garg*****

Abstract

Background: In 2016, Chikungunya infection presented in Western UP as an epidemic with many patients suffering from severe arthralgia. Chikungunya polyarthralgia/polyarthritis occurs more often in the hands, wrists, interphalangeal joints, feet and ankles but may also affect large joints such as the shoulders and knees. Chikungunya is usually self-limiting, however, in 30 to 40% of those infected, persistent polyarthritis/polyarthralgia may persist for months or even years.

Methods: This two-centre randomised study was conducted from October 2016 to January 2017 in the Medicine departments of LLRM Medical College and Subharti Medical College, Meerut. 150 adult patients with classical features of fever and joint pain, with inflammatory polyarthritis affecting both major and/or minor joints of upper and/or lower limbs, who were found eligible, were enrolled.

Out of the 150 patients, 75 patients (group A) were started on Aceclofenac at a dose of 200 mg/day in two divided doses. The other 75 patients (group B) were given oral corticosteroids in the form of tab methylprednisolone 4 mg PO for 4 days which was then tapered to 2 mg PO over the next 4 days. The intersity of pain at the time of enrolment, after 8 days and after 18 days was assessed with the help of Visual Analogue Score (VAS).

Results: Significant (P < 0.001) reduction in VAS scores was observed in group B, compared to group A.

Conclusion: Treatment with methylprednisolone reduced pain significantly in patients with post-chikungunya arthritis compared to aceclofenac given alone in the management for the same.

Introduction

Chikungunya virus (CHIKV) is an arbovirus, spread predominantly by *Aedes aegypti* and *Aedes albopictus* mosquitoes. Following an incubation period of 2 - 7 days, approximately 95% of infected people will develop symptoms. These consist of high fever, headaches, rash, myalgia and severe joint pain for which the virus was named. "Chikungunya" is a Makonde word in Tanzania meaning "to walk bent over" or "that which bends up"[1]. Polyarthralgia/polyarthritis is usually bilateral and symmetrical and occurs more often in the hands, wrists, interphalangeal joints, feet and ankles but may also affect large joints, such as the shoulders and knees[2]. Periarticular swelling is frequently observed. A maculopapular rash and facial swelling are present in approximately 40 to 50% of patients[3]. Additionally, while less common, severe manifestations including gastrointestinal disease, neurologic complications including meningoencephalitis and seizures, cardiovascular disease, uveitis, toxic hepatitis, haemorrhagic manifestations and death have been reported.These severe manifestations are more frequent in children, the elderly and people that have underlying comorbidities[4]. Chikungunya is usually self-limiting, with clinical manifestations regressing within a few weeks. However, in a percentage of those infected, which can vary from 30 to 40%, persistent polyarthritis/polyarthralgia, accompanied by morning stiffness and fatigue may persist for months or even years[5,6,7,8].

There is currently no specific antiviral treatment or vaccine for Chikungunya fever. Symptomatic treatment is the only recourse in the acute phase of the disease. This consists predominantly of rest, antipyretics and analgesics[9]. Unfortunately, efficacy data for most treatment regimens are lacking[10]. Non-steroidal anti-inflammatory drugs (NSAIDs) remain the mainstay of symptomatic treatment in Chikungunya arthritis. They help by relieving pain and inflammation associated with joint involvement and by reducing fever[11,12]. Often paracetamol is co-administered with other NSAIDs for enhanced antipyretic effect. However, their efficacy\ can be quite variable, and resolution of acute arthralgia can occur with or without their use. Similarly, NSAIDs can have variable effects in chronic cases. In some cases joint pain may resolve, but stiffness remains, perhaps suggesting permanent alterations in articular or peri-articular tissues resulting in decreased mobility[13]. It should also be noted that aspirin is not recommended due to bleeding

Assistant Professor, **Associate Professor, ***Professor, ****Junior Resident, Department of Medicine, LLRM Medical College, Garh Road, Meerut, Uttar Pradesh.

Corresponding Author: Dr Shweta Sharma, Assistant Professor, Department of Medicine, L-10, LLRM Medical College, Garh Road, Meerut, Uttar Pradesh. Tel: 9639282582, E-mail: drshwetadhanveer@gmail.com.

risk[14]. Because of the similarities between chronic CHIKV-associated arthralgia and rheumatoid arthritis, some disease modifying anti-rheumatoid drugs (DMARDs) such as hydroxychloroquine methotrexate, sulfasalazine and leflunomide have been utilised.There is no specific proven antiviral treatment, but ribavirin and interferon-alpha have been reported to have a possible useful role during the disease states. But again, the efficacy of these drugs are unclear[15].

Systemic corticosteroids, given on a short-term basis, are also beneficial in treatment of arthritis. Even though it is not specific, corticosteroids produce better relief from symptoms. While corticosteroid treatment is usually not recommended due to the potential for a rebound of arthritis and tenosynovitis, after therapy is ended, in severe cases of inflammatory polyarthritis refractory to NSAID, this modality of treatment can be attempted[16-18].

Methods

This two-centre randomised study was conducted from October 2016 to January 2017 in the Departments of Medicine, LLRM Medical College, Meerut and Subharti Medical College, Meerut. 150 adult patients with classical features of sudden onset of fever and joint pains, with inflammatory polyarthritis affecting both major and/or minor joints of upper and/or lower limbs persisting for atleast 15 days despite being on analgesics, were considered for enrolment. All patients gave a voluntary informed consent prior to screening. Patients were excluded if they had any of the following: significant renal and hepatic impairment, allergy to NSAIDs, pregnancy and lactation, diabetes mellitus, rheumatoid arthritis, osteoarthritis, gout, gastric or duodenal ulcers.

On first presentation, all patients were screened for their eligibility for participation. Demographic details of the patients including the age, sex, pulse rate, blood pressure, and body temperature were recorded. Duration (days) and type (continuous/remittent/intermittent) of fever, and duration of joint pain (days) and number (mono/oligo/ poly), type (small/large/mixed) and patterns (symmetrical/ asymmetrical) of joint involvement were recorded. Complete blood count and urine routine investigations, bleeding time, clotting time, liver function tests, renal function tests, rheumatoid factor, c-reactive protein, antinuclear antibody, IgM qualitative ELISA for chikungunya, electrocardiogram and chest X-ray were performed for eligibility assessment.Those found eligible were enrolled for the study.

Out of the 150 patients, 75 patients (group A) were started on NSAIDs. Aceclofenac was used in this study at a dose of 200 mg in two divided doses. The other group (group B) comprising of the remaining 75 patients was given oral corticosteroids in the form of tab methylprednisolone 4 mg PO for 4 days which was then tapered to 2 mg PO for the next 4 days and then stopped. Ethical clearance was taken from the ethics committee of the two institutions. The intersity of pain at the time of enrolment and pain relief after 8 days, and 18 days, was assessed with the help of Visual Analogue Score (VAS) score.

Table I: Baseline profile of the two groups.

	(Mean ± SD)	(Mean ± SD)	P - value
Clinical	**Group A**	**Group B**	
Male/female	17/58	16/59	
Age (years)	29.58 ± 8.1	30.09 ± 7.6	0.554
Duration of fever (days)	9.53 ± 7.40	9.33 ± 3.54	0.758
Duration of joint pain (days)	21.34 ± 4.52	22.49 ± 4.16	0.992
VAS at visit	8.05 ± 1.50	7.50 ± 1.64	0.280
Laboratory			
Haemoglobin (g/dl)	10.56 ± 1.05	10.83 ± 1.39	0.063
Total WBC count (cells/mm^3)	6,450.00 ± 1,078	6,395. ± 1175.	0.216
Bleeding time (min)	4.33 ± 0.5	4.65 ± 0.45	0.061
Clotting time (min)	1.80 ± .33	1.75 ± 0.30	0.113
Blood urea (mg/dl)	23.27 ± 8.65	24.59 ± 11.30	0.342
Serum creatinine (mg/dl)	0.82 ± 0.65	0.90 ± 0.94	0.052
Serum bilirubin (mg/dl)	0.61 ± 0.26	0.72 ± 0.14	0.337
SGOT (IU/L)	44.30 ± 12.50	52.60 ± 16.30	0.769
SGPT (IU/L)	32.40 ± 11.80	37.20 ± 13.10	0.648
Alkaline phosphatase (IU/L)	93.80 ± 26.70	105.40 ± 52.10	0.057
CRP (mg/l)	3.92 ± 4.75	4.38 ± 3.88	0.232

Results

The study period was from October 2016 to January 2017. One hundred and fifty patients (75 patients per arm) were enrolled in the study.The baseline demographic and clinical features of patients in the treatment groups are given in Table I. There was no significant difference in baseline characteristics between the groups.

All 150 patients completed the study.VAS scores showed a significant ($P < 0.001$) reduction at the end of treatment compared to baseline, in group B, using ANOVA. Table II shows the visit-wise change in mean VAS scores in both the arms. Even though there was an overall diminishing trend in VAS scores in both the groups, there was an increasing trend of lower VAS in the study group who were on oral corticosteroids (group B), which persisted, even 10 days after the therapy was stopped.

Table II: Visit-wise VAS scores in the control (group A) and study (group B) groups.

Visit	Group A	Group B	P value
Visit 1 (Day = 0)	8.05 ±1.50	7.50±1.64	0.280
Visit 2 (Day = 8)	7.31+0.82	2.92+0.73	0.000*
Visit 3 (Day = 18)	7.45+1.12	2.96+0.83	0.000*

**Significant difference between groups.*

Discussion

There is minimal evidence-based research regarding the treatment of Chikungunya-associated rheumatic syndromes. Notwithstanding the increasing number of chikungunya diagnoses, there is no guideline-based recommendation for its management[19]. There is no specific antiviral therapy or preventive vaccine. Management objective, then, is to control fever, decrease the impact of stamulated immune process control pain, eliminate oedema, minimise the effects of rash and prevent the appearance of chronic joint injuries. Currently, specific treatment modalities for acute and chronic CHIKV-induced disease do not exist, and the majority of treatment plans consist of supportive and symptomatic care. In acute stages of the disease, this consists predominantly of rest, antipyretics and analgesics. Unfortunately, efficacy data for most treatment regimens are lacking. Most rely on non-steroidal anti-inflammatory drugs (NSAIDs), whose efficacy can be quite variable, and resolution of acute arthralgia can occur with or without their use . Similarly, NSAIDs can have variable effects in chronic cases. In one study in Bangladesh, 2 of 6 patients treated acutely with NSAIDs had persistent pain at 2 - 3 months. In some cases joint pain may resolve, but stiffness remains perhaps suggesting permanent alterations in articular or peri-articular tissues resulting in decreased mobility. Nevertheless, physicians must be aware of possible severe adverse effects such as aspirin-induced bleeding or paracetamol induced fulminant hepatitis in patients with underlying chronic liver disease. There are many other treatments under investigation during the acute phase but none has yet been approved. In a 1984 study, Brighton found that Chloroquine may be beneficial for the treatment of chronic arthritis/arthralgia; however, when used in the acute stage, it did not benefit[20]. Naproxen, methotrexate, and hydroxychloroquine have also been used with some success in some patients.

Regarding the pathophysiology of arthralgia/arthritis in CHIKV infection, a study by researchers at the Singapore Immunology Network and the Communicable Diseases Center (CDC) have found a strong positive correlation between the amount of chikungunya virus (known as the viral load) present in the body of patients and the level of inflammatory cytokines[21]. The finding could help explain why the majority of patients with chikungunya fever are plagued by persistent joint pain.

Patients with chikungunya-related musculoskeletal disorders, with polyarthralgia involving hands and feet typically benefit from the use of short steroid cycles. It is known that corticosteroids act by decreasing the inflammatory phenomenon and blocking the immune system and also inhibit the expression and action of most cytokines, especially in the acute phase of the disease. There is no consensus with regard to the best management regimen; however, some authors recommend oral prednisone in the dose of 40 to 60 mg/day for three to five days. One alternative would be 4 mg oral or parenteral dexamethasone every 8 hourly for three days and in refractory cases intra-articular corticosteroids application. We have used oral methylprednisolone therapy in our patients in minimal doses to minimise the side-effects of steroid treatment.

Conclusion

In our two-centre study, we found that a short course of oral corticosteroids led to better pain relief and quality of life than NSAIDS in patients with post chikungunya arthritis. We hence, recommend addition of this regimen in the management of individuals suffering from adverse quality of life due to post-chikungunya arthiritis.

References

1. Chopra A, Anuradha V, Lagoo-Joshi V *et al*. Chikungunya virus aches and pains: an emerging challenge. *Arthritis Rheum* 2008; 58 (9): 2921-2.
2. Pialoux G, Gauzere BA, Jaureguiberry S *et al*. Chikungunya, an epidemic arbovirosis. *Lancet Infect Dis* 2007; 7 (5): 319-27.
3. Thiberville SD, Boisson V, Gaudart J *et al*. Chikungunya fever: a clinical and virological investigation of outpatients on Reunion Island, South-West Indian Ocean. *PLoS Negl Trop Dis* 2013; 7 (1).
4. Labadie K, Larcher T, Joubert C *et al*. Chikungunya disease in nonhuman primates involves long-term viral persistence in macrophages. *J Clin Invest* 2010; 120 (3): 894-906.
5. Sissoko D, Malvy D, Ezzedine K *et al*. Post-epidemic Chikungunya disease on Reunion Island: course of rheumatic manifestations and associated factors over a 15-month period. *PLoS Negl Trop Dis* 2009; 3 (3): e389.
6. Schilte C, Staikowsky F, Couderc T *et al*. Chikungunya virus-associated long-term arthralgia: a 36-month prospective longitudinal study. *PLoS Negl Trop Dis* 2013; 7 (3): e2137.
7. Borgherini G, Poubeau P, Jossaume A *et al*. Persistent arthralgia associated with chikungunya virus: a study of 88 adult patients on reunion island. *Clin Infect Dis* 2008; 47 (4): 469-75.
8. Chopra A, Anuradha V, Ghorpade R *et al*. Acute Chikungunya and persistent musculoskeletal pain following the 2006 Indian epidemic: a 2-year prospective rural community study. *Epidemiol Infect* 2012; 140 (5): 842-50.

9. Ali Ou Alla S, Combe B. Arthritis after infection with Chikungunya virus. *Best Pract Res Clin Rheumatol* 2011; 25 (3): 337-46.
10. Khasnis AA, Schoen RT, Calabrese LH. Emerging viral infections in rheumatic diseases. *Semin Arthritis Rheum* 2011; 41 (2): 236-46.
11. Mizuno Y, Kato Y, Takeshita N *et al*. Clinical and radiological features of imported chikungunya fever in Japan: a study of six cases at the National Center for Global Health and Medicine. *J Infect Chemother* 2011; 17 (3): 419-23.
12. Hassan R, Rahman MM, Moniruzzaman M *et al*. Chikungunya - an emerging infection in Bangladesh: a case series. *J Med Case Reports* 2014; 8: 67.
13. Volpe A, Caramaschi P, Angheben A *et al*. Chikungunya outbreak remember the arthropathy. *Rheumatology (Oxford)* 2006; 45 (11): 1449-50.
14. Bouquillard E, Combe B. A report of 21 cases of rheumatoid arthritis following Chikungunya fever. A mean follow-up of two years. *Joint Bone Spine* 2009; 76 (6): 654-7.
15. Foissac M, Javelle E, Ray S *et al*. Post-Chikungunya rheumatoid arthritis, Saint Martin. *Emerg Infect Dis* 2015; 21 (3): 530-2.
14. Cavrini F, Gaibani P, Pierro AM *et al*. Chikungunya: an emerging and spreading arthropod-borne viral disease. *J Infect Dev Ctries* 2009; 3 (10): 744-52.
15. Simon F, Javelle E, Cabie A *et al*. French guidelines for the management of chikungunya (acute and persistent presentations). November 2014. *Med Mal Infect* 2015; 45 (7): 243-63.
16. Chikungunya Virus Advances in Biology, Pathogenesis, and Treatment Editors: Okeoma, Chioma M. (Ed.) pg 12.
17. Cavrini F, Gaibani P, Pierro AM *et al*. Chikungunya: an emerging and spreading arthropod-borne viral disease. *J Infect Dev Ctries* 2009; 3 (10): 744-52.
18. Simon F, Javelle E, Cabie A *et al*. French guidelines for the management of chikungunya (acute and persistent presentations). November 2014. *Med Mal Infect* 2015; 45 (7): 243-63.
19. Specific Management of Post-Chikungunya Rheumatic Disorders: A Retrospective Study of 159 Cases in Reunion Island from 2006-2012 Emilie Javelle,, Anne Ribera, Isabelle Degasne, Bernard-Alex Gaüzère, Catherine Marimoutou, and Fabrice Simon.
20. Brighton SW. Chloroquine phosphate treatment of chronic Chikungunya arthritis. An open pilot study. *S Afr Med J*. 1984; 66 (6): 217-8.
21. Immune Response Causes Joint Pain in Chikungunya Patients Read more from Asian Scientist Magazine at: https://www.asianscientist.com/2011/05/health/immune-response-joint-pain-chikungunya-patients/Accessed on 11th October 2016.