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*Original Article*

# Comparison of an intravenous pulse of methylprednisolone versus oral corticosteroid in severe acute rheumatic carditis: a randomized clinical trial

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**Abstract** *Objectives:* To compare the short-term prognosis of patients with severe acute rheumatic carditis when treated with an intravenous pulse of methylprednisolone in comparison with conventional treatment using oral prednisone. *Methods:* We designed a randomized clinical trial in the setting of a university general hospital in Brazil. We randomly allocated 18 patients with the diagnosis of severe acute rheumatic carditis and congestive heart failure to receive an intravenous pulse as opposed to oral prednisolone. Methylprednisolone was administered in a dose of 1 g intravenously for 3 consecutive days in the first and second weeks, for two days in the third, and one day in the fourth week. Prednisone was administered in a dose of 1.5 mg/kg/day over the period of 4 weeks. *Results:* The mean age of the patients was 11.1 ± 3.7 years, with a median of 12 years. Patients on oral treatment showed a more pronounced decrease in the heart rate, sedimentation rate, and in the titres of C-reactive protein than those receiving intravenous therapy. At the end of treatment, a mild decrease in the left ventricular end-systolic dimension was found in those having oral treatment, compared to an increase in the group having intravenous treatment ($p = 0.036$). The ejection fraction showed a median increase of 5% in those undergoing oral treatment, and a median decrease of 6% in the group with intravenous therapy ($p = 0.009$). There were 5 therapeutic failures in those receiving intravenous therapy (56%), including 1 death. Therapeutic failures were not observed in those treated orally ($p = 0.03$). *Conclusion:* Intravenous treatment of methylprednisolone, as a single anti-inflammatory agent, was inferior to conventional treatment with oral prednisone in the control of severe rheumatic carditis.

Keywords: Rheumatic fever; carditis; corticosteroids; pulse therapy

ACUTE RHEUMATIC FEVER AND ITS COMPLICATIONS are much more common in developing countries, like Brazil, when compared to more industrialized regions.[1–4] In this respect, in many places, chronic rheumatic heart disease is still the most frequent cause of severe cardiac problems and the need for cardiac surgery in young people.[5] Furthermore, mortality continues to be high, up to 12%, during the course of the acute rheumatic process.[6–12]

There is some evidence that treatment with oral corticosteroids, in the short term, improves the prognosis of patients with acute rheumatic carditis.[13–15] Due to the severity of the problem, however, it is always necessary to assess new therapeutic strategies. In other rheumatic diseases, particularly in severe systemic lupus erythematosus, there is evidence that an intravenous pulse of methylprednisolone is more efficacious than oral corticosteroids.[16–18] Experience with such an intravenous pulse in acute rheumatic fever is small,[19–22] albeit that the studies thus far conducted suggested an advantage of intravenous over oral prednisone. The allocation of the patients to treatments, however, was not randomized. The potential influence of selection on the results described by

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these authors, therefore, limits the potential for drawing definite conclusions. For these reasons, we developed the present study as a randomized clinical trial, comparing the short-term prognosis of severe acute rheumatic carditis in patients allocated to receive an intravenous pulse of methylprednisolone as opposed to those undergoing conventional treatment with oral prednisone.

## Materials and methods

We randomly assigned 18 patients admitted between 1990 and 1991 to Professor Edgard Santos Hospital of the University of Bahia, Brazil, with the diagnosis of acute rheumatic carditis and congestive heart failure to receive either an intravenous pulse of methylprednisolone or oral prednisone. Of the patients, six were in the third functional class of the classification made by the New York Heart Association, while 12 were in the fourth class. We used the Jones' modified criterions to make the diagnosis of acute rheumatic fever and carditis.[23] In keeping with the predefined criterions, all patients had developed heart failure within 30 days in the absence of other precipitating factors, besides exhibiting rheumatic carditis, presence of a pericardial rub, or a progressive increasing of the heart volume in a chest radiography, and at least two minor manifestations of rheumatic fever, or another major plus a minor manifestation in patients with evidence of recent streptococcal infection. The diagnosis of congestive heart failure was based on clinical findings, such as dyspnea plus objective evidence of pulmonary vascular congestion, a protodiastolic gallop, jugular venous distention, or painful hepatomegaly. Patients who had used corticosteroids in the last 8 weeks were excluded.

The research protocol was approved by the ethics committee and by the faculty of the Paediatrics Department of the School of Medicine of the Federal University of Bahia. A verbal consent to participate in the study was obtained from the parents, and from the children or adolescents when appropriate.

### *Baseline clinical characteristics*

The age of the patients ranged from 4 to 18 years, with mean and standard deviations, of 11.1 ± 3.7 years, and a median of 12 years. The means of age did not differ significantly ($p = 0.252$) between those receiving oral (12.4 ± 2.7 yr) as opposed to intravenous (10.1 ± 4.6 yr) therapy (Table 1). There were 5 (55.6%) females in those having oral medication, and 6 (66.7%) in those allocated to the intravenous group.

The severity of the congestive heart failure assessed according to the criterions of the New York Heart Association did not vary significantly between the groups (Table 1). Previous episodes of acute rheumatic fever had occurred in 3 patients receiving intravenous therapy, and in four undergoing oral treatment.

The distribution and the severity of valvar lesions in the 2 groups, based on color Doppler echocardiography, are shown in Table 2. Mitral insufficiency

Table 1. Baseline clinical, laboratory and echocardiographic characteristics.

| | Intravenous | Oral | |
|---|---|---|---|
| Age (yr) | 10.1 + 4.6 | 12.4 + 2.6 | NS |
| Sex (M/F) | 3/6 | 4/5 | NS |
| FC III/IV (N.Y.H.A.) | 9 (100%) | 9 (100%) | NS |
| HR (bpm) | 119.3 ± 21.2 | 123.5 ± 9.0 | NS |
| ESR (mm/h) | 49.5 ± 12.9 | 53.8 ± 9.9 | NS |
| CRP+++/++++ | 8 (89%) | 6 (67%) | NS |
| LVEDD (mm) | 56.0 ± 7.0 | 62.9 ± 7.5 | 0.07 |
| LVESD (mm) | 34.9 ± 3.6 | 43.6 ± 9.0 | 0.04 |
| EF (%) | 66.0 ± 10.8 | 57.1 ± 13.2 | 0.09 |

Abbreviations: CRP: C-reactive protein; EF: left ventricular ejection fraction; ESR: erythrocyte sedimentation rate; FC: functional class; HR: heart rate; LVEDD: left ventricular end-diastolic dimension; LVESD: left ventricular end-systolic dimension

Table 2. Type and severity of the valvar lesions.

| | Intravenous therapy | | | | | | Oral therapy | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pts. | MR | MS | AR | AS | TR | TS | MR | MS | AR | AS | TR | TS |
| 1 | ++++ | – | ++ | – | + | – | +++ | – | ++ | – | + | – |
| 2 | ++++ | – | – | – | – | – | ++++ | – | +++ | – | +++ | – |
| 3 | ++++ | – | – | – | – | – | ++++ | – | ++ | – | + | – |
| 4 | ++++ | – | ++ | – | + | – | ++++ | – | + | – | ++ | – |
| 5 | ++++ | – | – | – | + | – | ++++ | – | – | – | + | – |
| 6 | +++ | – | + | – | + | – | ++++ | – | ++++ | – | + | – |
| 7 | ++++ | + | + | + | + | – | +++ | – | + | – | + | – |
| 8 | + | – | ++++ | – | – | – | ++++ | + | ++ | – | + | – |
| 9 | – | ++++ | + | – | +++ | – | +++ | – | ++++ | – | – | – |

Abbreviations: AR: aortic valve regurgitation; AS: aortic valve stenosis; MR: mitral valve regurgitation; MS: mitral valve stenosis; TR: tricuspid valve regurgitation; TS: tricuspid valve stenosis; +: mild; ++: moderate; +++: moderate/severe; ++++: severe

was the most frequent and the most severe valvar lesion in both groups.

*Intervention*

In those having oral treatment, prednisone was used in a dose of 1.5 mg/kg/day during four consecutive weeks. In the group having intravenous treatment, methylprednisolone was used at a dose of 1 g/day, or 30 mg/kg/day in children weighing less than 30 kg. The treatment was given for 3 days in the 1st and 2nd weeks, 2 days in the 3rd week and 1 day in the 4th week. This plan of treatment was the same as used in previous studies.[19,20] All patients in both groups were also treated with digoxin, furosemide and captopril. Benzathine penicillin was administered to each patient to eradicate oropharyngeal streptococcus. No patient received anticoagulant, antiarrhythmic or antihypertensive drugs before randomization or during the study.

*Echocardiogram*

A complete cross-sectional echocardiogram with color Doppler study was obtained in every patient, using the Siemens model Sonoline CF equipment, before treatment, in the 2nd week, and at end of the 4th week of treatment, or when a diagnosis of therapeutic failure was considered. The tests were performed by different observers blinded to the mode of treatment, and also to the clinical data. They were recorded on videotape for subsequent analysis. We measured left ventricular end-diastolic and end-systolic dimensions, septal and posterior wall thickness, left atrial dimension, left ventricular shortening fraction and left ventricular ejection fraction.

*Laboratory investigation*

We analysed the white blood cell count, haematocrit, hemoglobin, erythrocyte sedimentation rate, C-reactive protein, antistreptolysin O, electrocardiogram and chest X-ray at least 3 times during follow-up: before the initiation of the treatment, in the 2nd week, and at the end of the 4th week of treatment or when therapeutic failure was diagnosed.

*Criterions for diagnosis of therapeutic failure*

The criterions used for therapeutic failure were: persistence without significant improvement or return of a major manifestation, such as congestive heart failure, arthritis, plus at least one minor manifestation after two weeks of treatment, and death.

*Statistical analysis*

The quantitative variables were measured according to the mean and standard deviations and the median. For statistical analysis, clinical, laboratory and echocardiographic data were considered only at baseline and at the end of treatment in the 4th week. In two of the patients with the diagnosis of therapeutic failure, the data used for comparison were those obtained in the 3rd week of treatment, before crossover to oral corticosteroid.

The Mann–Whitney and the Fisher's exact tests were used to compare quantitative and categorical data, respectively, between the two groups. All statistical analyses were performed using the Statistical Package for Social Science software, version 9.0 for Windows. Statistical tests of significance were two-tailed.

## Results

*Clinical and laboratory data during follow-up (Table 3, Fig. 1)*

By comparing the baseline and the last measurement, an improvement in clinical and laboratorial parameters was observed in all patients, particularly in those allocated to oral treatment. On average, the heart rate decreased by 12.87 ± 17.3 beats per minute, with a median of 11.0 beats, in the group allocated to intravenous treatment, and by 35.22 ± 19.3 beats, with a median of 40 beats, in those receiving oral steroids ($p = 0.034$) (Fig. 1). The erythrocytic sedimentation rate decreased by 14.5 ± 20.5 mm/h, with a median of 12.5 mm/h, in those treated intravenously, and by 36.5 ± 13.0 mm/h, with a median of 37.0 mm/h, in those dosed orally ($p = 0.016$). Of the patients treated orally, 8 improved at least 2 points in functional class (89%) compared to two patients (22%) in the group receiving intravenous therapy ($p = 0.015$). The C-reactive protein remained positive in all patients treated intravenously, but in only 4 of the 9 patients having oral steroids ($p = 0.029$).

Table 3. Comparisons of the therapeutic response between groups (from the baseline to the end of evaluation of treatment).

| | Intravenous | Oral | p |
|---|---|---|---|
| HR reduction (bpm) | 12.87 ± 17.3 | 35.22 ± 19.3 | 0.034 |
| FC reduction >2 | 2 (22%) | 8 (89%) | 0.015 |
| ESR reduction (mm/h) | 14.5 ± 20.5 | 36.5 ± 13.0 | 0.016 |
| CRP Negativation | 0 | 5 (55.6%) | 0.029 |
| LVEDD (mm) | +1.86 ± 7.2 | −1.5 ± 4.2 | 0.3 |
| LVESD (mm) | +3.28 ± 5.7 | −3.87 ± 5.5 | 0.036 |
| EF% | −4.86 ± 5.1 | +5.87 ± 8.0 | 0.009 |

Data are described as means ± SD.
Abbreviations: CRP: C-reactive protein; EF%: left ventricular ejection fraction; ESR: erythrocyte sedimentation rate; FC: functional class; HR: heart rate; LVEDD: left ventricular end diastolic dimension; LVESD: left ventricular end systolic dimension

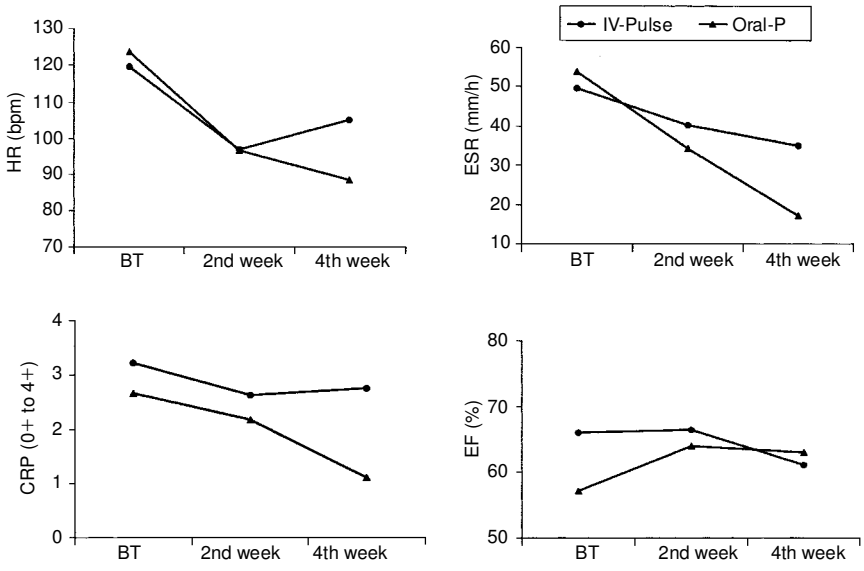


**Figure 1.**
*Results of treatment. The data are described as mean ± SD. BT = before treatment; CRP = C-reactive protein; EF = ejection fraction; ESR = erythrocyte sedimentation rate; HR=heart rate.*

Treatment failed on five occasions (56%) when administered intravenously, with no failures in those receiving oral steroids ($p = 0.03$). In the former group, 2 patients persisted with congestive heart failure, a fast heart rate and raised levels of erythrocytic sedimentation rate and C-reactive protein, between the 3rd and 4th weeks of treatment. Also in this group was a patient with arthritis, fever, sinus tachycardia, and raised erythrocytic sedimentation rate and C-reactive protein, along with another patient having fever and signs of active carditis with a heart rate of 144 beats per minute at the fourth week of treatment. All patients who failed to respond to intravenous therapy made a significant improvement, based on clinical and laboratory parameters, after the introduction of oral prednisone in conventional doses. They were discharged without signs of rheumatic activity. One eight-year old with severe carditis developed acute pulmonary edema and died within the first day of treatment with intravenous methylprednisolone, in the absence of cardiac arrhythmias, electrolytic abnormalities or other factors that could be implicated as a cause of death. There was no difference in the doses of methylprednisolone given to patients who had therapeutic success and those who failed with intravenous therapy.

### *Echocardiographic data*

At baseline, the left atrial dimension, the ejection fraction, and the shortening fraction were similar between those receiving oral and intravenous treatment. The left ventricular end-diastolic and end-systolic dimensions were slightly decreased in the patients treated intravenously (57 ± 9.2 mm versus 64 ± 7.4 mm, and 38 ± 8.9 mm versus 44 ± 8.5 mm, respectively) (Table 1). By comparing the first to the last measurement, we found a mean decrease of 3.87 ± 5.5 mm, with a median of 3.5 mm, in the left ventricular end-systolic dimension among the patients treated orally. In contrast, the left ventricular end-systolic dimension increased in those receiving intravenous therapy (3.28 ± 5.7 mm, median + 5.0 mm − $p = 0.036$). The ejection fraction increased by 5.87 + 8.0%, with a median of + 5.0%, in those treated orally, but decreased by 4.86 ± 5.1%, with a median of −6.0%, in the other group ($p = 0.009$) (Table 3 and Fig. 1). The left ventricular end-diastolic dimension, and the left atrial dimension, did not change significantly in either group between the first and the last measurements.

## Discussion

Our data show that conventional treatment with oral prednisone has a better short-term efficacy than an intravenous pulse of methylprednisolone when given to patients with severe acute rheumatic carditis. These results are in disagreement with those from previous studies that suggested a better response to intravenous therapy.[19–22] The results of these previous studies, however, could be due to selection bias, considering that the allocation of treatment was not randomized. It is also important to note that, in the present study, the better response to the conventional treatment with prednisone was observed for

clinical, laboratory, and echocardiographic parameters. Moreover, except for the one fatal case, all patients who failed to respond to pulsed intravenous methylprednisolone had a rapid improvement after the introduction of oral prednisone in conventional doses. According to the clinical and laboratory data, the rheumatic carditis was controlled in all our patients receiving oral treatment.

Our results, therefore, support for most patients the conventional treatment of acute rheumatic carditis. This consists of eradicating oropharyngeal streptococcal infection with penicillin, and giving an orally administered corticosteroid, mostly usually prednisone. Exceptions would be patients unable to ingest orally because of vomiting or other reasons, or those rare patients refractory to the conventional treatment with prednisone. The addition of intravenous methylprednisolone may be beneficial in these situations.[24,25] It should be observed that our patients were followed only during their period of hospitalization. According to the published data, treatment with corticosteroids is important in preventing death during episodes of carditis, but does not prevent chronic lesions of the cardiac valves.[26–30]

It is unlikely that the worse prognosis in those treated intravenously was due to differences in the severity of the carditis between groups, since the baseline clinical and laboratory characteristics were similar in all the patients. The pharmacological effects of pulsed intravenous therapy with methylprednisolone upon the immunoglobulins and lymphocytes has been reported to persist for days or weeks.[31] It is possible, however, that the longer interval of days without medication between the pulses of methylprednisolone, more pronounced after the 3rd week of therapy, may decrease the anti-inflammatory and immunomodulator effects, promoting only a partial control of the disease process.

Lang and Dooley[32] reported that intravenous pulsed therapy with methylprednisolone failed in the treatment of juvenile dermatomyositis. They postulated that the intermittent nature of pulsed therapy, similar to alternate-day oral therapy, results in it being less effective than daily corticosteroid treatment in the majority of children with juvenile dermatomyositis. Most trials evaluating the therapeutic efficacy of intravenous pulses of methylprednisolone have been uncontrolled. In a controlled study, nonetheless, intravenous pulsed therapy with methylprednisolone was found to be less effective than pulsed therapy with cyclophosphamide in lupus nephritis.[33]

Consideration should also be given to the doses of methylprednisolone administered in children. Herdy et al.[21] reported unsuccessful results with a dose of 20 mg/kg/day. We administered the dose usually given to children with other rheumatic diseases, namely 30 mg/kg/day for those weighing less than 30 kg, and 1 g for those weighing more than 30 kg.[34] Furthermore, in our study, the doses of methylprednisolone were similar in children who had a good response and those who had a therapeutic failure.

Our current data, therefore, do not support the suggestion of using the intravenous methylprednisolone given as high dose pulses as the initial option for treatment of patients with severe acute rheumatic carditis. According to the results of this randomized clinical trial, intravenous pulses of methylprednisolone were inferior to the conventional oral treatment with prednisone in controlling rheumatic carditis. Further investigations, however, are needed to confirm our results.

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