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Research Article

Single Versus Divided-Dose Steroids in Treatment of Rheumatic Carditis

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Abstract

Introduction: Patients with rheumatic carditis and more than minimal cardiomegaly and/or congestive heart failure should receive corticosteroids. The usual dose of prednisolone is two mg/kg/day in four divided doses. We aim by this study to compare the regimen of giving steroids in a single daily dose with that of giving them in four-divided doses.

Patients and Methods: The study was conducted on 24 patients having rheumatic carditis. 12 patients were started on prednisolone at a dose of two mg/kg/day in a single daily dose. The other 12 patients were started on prednisolone at a dose of two mg/kg/day in four divided doses.

Results: There was no significant statistical difference between the two groups of patients as regard the duration of treatment before remission. No complications related to steroids were observed in any of our patients.

Conclusion: Prednisolone, as a single morning dose is as effective as divided doses for treatment of rheumatic carditis with no higher risk of complications. As single-dose steroid therapy is likely to be associated with better drug compliance, we recommend it as the regimen of choice for treatment of rheumatic carditis.

Keywords: *Rheumatic Carditis; Prednisolone; Group A Streptococcal (GAS); Acute Rheumatic Fever (ARF)*

Introduction

Repeated group A streptococcal (GAS) infections are thought to occur and prime the immune response before the first episode of acute rheumatic fever (ARF). Symptoms of arthritis, carditis, erythema marginatum, subcutaneous nodules, or chorea usually present one to three weeks after GAS pharyngitis. In recent outbreaks in the United States (US), affected patients reported only mild pharyngitis, for which only a few sought medical attention. Risk factors are poorly understood but likely include host factors such as susceptibility to the immune response to group A streptococci (limited to 3% to 6% of the population); housing and overcrowding remain important considerations [1].

ARF is a multisystem autoimmune inflammatory disorder. Severe carditis in the first episode or in recurrent attacks of ARF can lead to rheumatic heart disease (RHD) which is a chronic valvulopathy [2].

ARF has become considerably less common in the developed world over the last half-century. However, studies in developing countries have revealed that it still occurs frequently, and the resultant RHD is the source of substantial mortality. Indeed, in some developing countries ARF has caused nearly half of all admissions for heart disease in children, making it the most common cause of acquired heart disease in children [2]. The studies reported incidence of ARF per year ranging from 0.1 per 100,000 in Greece to 826 per 100,000 in Sudan [3]. The highest prevalence of RHD is found in sub-Saharan Africa, South Central Asia and the Pacific [2].

Because no clinical or laboratory finding is pathognomonic for ARF, T Duckett Jones, in 1944, proposed guidelines to aid in diagnosis. The Jones' Criteria, as revised in 2015 by the American Heart Association (AHA) (Table 1), is now intended for diagnosis of the initial attack of ARF and recurrent attacks. There are five major and four minor criteria and a requirement of evidence of recent GAS infection. Diagnosis of a first attack or recurrent attack of ARF can be established when a patient fulfills two major or one major and two minor criteria and has evidence of preceding GAS infection [4].

Major manifestations	Minor manifestations	Supporting evidence of antecedent GAS infection
Carditis Polyarthritis Erythema marginatum Subcutaneous nodules Chorea	Clinical features: • Arthralgia • Fever Laboratory features (elevated acute phase reactants): • Erythrocyte sedimentation rate • C-reactive protein Prolonged P-R interval	Positive throat culture or rapid streptococcal antigen test Elevated or increasing streptococcal antibody titer

Table 1: *Jones criteria, updated 2015 (Stanford, 2015).*

Carditis, valvulitis in particular, is the single most important cause of morbidity and mortality in rheumatic fever (RF) [5]. There is evidence of cardiac involvement during the acute episode in 40 - 80% of cases of ARF [6], but cardiac involvement almost always occurs in recurrent episodes [5]. Valvular heart involvement in the attack of RF may range from mild to severe and is suspected on the basis of a murmur on physical examination or unexplained cardiomegaly or heart failure [7], but non-invasive imaging with echocardiography increases the sensitivity of diagnosing valvular heart disease (VHD) since it is better than physical examination and should be used where available. About 90% of children who have carditis during RF episodes will develop chronic and progressive RHD from inflammation and scarring of the heart valves, which may result in haemodynamically significant valvular regurgitation and/or stenosis, heart failure, and death [5].

Patients with typical migratory arthritis and those with carditis without cardiomegaly or congestive heart failure should be treated with oral salicylates. Patients with carditis and more than minimal cardiomegaly and/or congestive heart failure should receive corticosteroids. The usual dose of prednisolone is two mg/kg/day in four divided doses [4].

Aim of the Work

Is to compare the regimen of giving steroids in a single daily dose with that of giving them in four-divided doses in treatment of rheumatic carditis, as regard the compliance, response to treatment, and occurrence of complications.

Patients and Methods

The study was conducted on 24 patients having rheumatic carditis whether initial or recurrent, admitted in the Cardiology Unit of Assiut University Children Hospital (AUCH), including 11 males (45.8%) and 13 males (54.2%). Most patients with ARF came directly to the outpatient clinic of AUCH, the others were referred from different hospitals and health units of the districts and villages of Assiut Governorate and other governorates of Upper Egypt. The ages of children ranged from 3.5 - 13y with a mean of 7.96 ± 3.29 years. Selection of these patients was accomplished as follow: patients suspected clinically to have an initial or recurrent RF with clinical carditis, based on Jones' criteria, were subjected to investigations including ESR, C-reactive protein assay, ECG, chest X-ray, echocardiography, and evidence of a recent GAS infection (ASO, other strepococcal antibody titer, or throat culture) to fulfill diagnosis of RF.

Inclusion criteria

- Initial or recurrent RF as defined by the revised Jones' criteria.
- Clinical carditis as evidenced by one or more of the following:
    - A significant apical pansystolic or diastolic murmur in a patient with no previous history of RF.
    - A change in the character of a pre-existing murmur or the development of a new murmur in a patient with a previous history of RF.
    - Pericarditis or pericardial effusion
    - Cardiomegaly
    - Congestive cardiac failure
- The severity of carditis was ascertained on the basis of clinical, radiographical, and echocardiographical data. Carditis was classified as:
    - Mild: Characterized by the presence of valvular insufficiency without cardiomegaly.
    - Moderate: Characterized by the presence of cardiomegaly.
    - Severe: If there was marked cardiomegaly or congestive cardiac failure [8].

Exclusion criteria

Cases of RF without clinical carditis

12 patients (group 1) were given prednisolone at a dose of 2 mg/kg/day in a single daily dose 2 - 3 weeks. Then, in improved cases (clinical remission, normal sleeping pulse, and negative CRP in cases with a previous positive test), prednisolone was tapered and discontiued while giving saicylates. Other lines of treatment (fluid restriction, salt restriction, diuretics, afterload-reducing agents and digoxin) were given when indicated.

The other 12 patients (group 2) were given prednisolone at a dose of 2 mg/kg/day in four divided doses for 2 - 3 weeks. The rest of the course of treatment was accomplished in a similar manner to the previous 12 patients.

Data entry was done by using the excel program and statistical analysis was done with SPSS software (V. 16 SPSS Inc., Chicago, Il, USA). The qualitative variables were summarized as percentages and the quantitative ones as means and standard deviations. Chi square test was used to compare the qualitative data. Two independent samples, Mann-Whitney test, was used to compare quantitative variables. P value < 0.05 was considered statistically significant.

Ethical considerations: The study was approved by the ethical committee, faculty of medicine, Assiut university.

Results

The study included 24 patients having moderate or severe rheumatic carditis, that deserves steroids for treatment. Their ages ranged from 3.5 to 13 years (mean ± SD: 7.96 ± 3.29). 11 were males (45.8%) and 13 were females (54.2%), males to females ratio was 1 : 1.2. 12 patients (5 males and 7 females) were treated by prednisolone in a single morning dose (group 1), while the other 12 patients (6 males and 6 females) were treated by prednisolone in four- divided dose (group 2). Table 2 shows the age (range and mean) and the sex distribution of both groups of patients. There is no significant statistical difference between them.

	Group 1 (n = 12)	Group 2 (n = 12)	p value
Age (y) Range Mean ± SD	 3.5 - 13 y 7.92 ± 3.42	 4 - 13y 8 ± 3.3	0.89 (ns)*
Sex (n and %) Male Female	 5 (41.7%) 7 (58.3%)	 6 (50%) 6 (50%)	1.00 (ns)**

Table 2: *Comparison between ages and male to female ratio of the two groups of patients.*

Ns: Non-Significant; n: Number

**Mann-Whitney test **Fisher's Exact Test*

Past history of recurrent acute tonsillitis or pharyngitis was present in 17 patients (70.83%), eight patients in group 1 (66.7%) and nine patients in group 2 (75%). Family history of ARF or RHD was positive in 5 patients (20.83%), three patients in group 1 (25%) and two patients in group 2 (16.7%). The present attack of ARF was initial one in 11 patients (45.8%), while it was recurrent in 13 patients (54.2%). Among the 13 patients having recurrent ARF, only one (in group 1) was regular on long-acting penicillin (LAP).

Table 3 shows that there is no significant statistical difference between the two groups of patients as regard past history of recurrent acute tonsillitis or pharyngitis, family history of ARF or RHD, type of ARF attack, and regularity on LAP among patients having recurrent ARF.

	Group (1)		Group (2)		P value
	n	%	n	%	
Past history of recurrent acute tonsillitis or pharyngitis	8	66.7	9	75	1.00 (ns)
Family history of RF or RHD	3	25	2	16.7	1.00 (ns)
Type of ARF attack:					
• Initial	6	50	5	41.7	1.00 (ns)
• 2-Recurrent	6	50	7	58.3	
Regularity on LAP:					
• Regular	1	16.7	0	0	0.46 (ns)
• Not regular	5	83.3	7	100	

Table 3: *Comparison between the two groups as regard historical findings.*

Fisher's Exact Test

As regard major Jones' criteria other than carditis, arthritis occurred in seven patients (29.2%), four in group 1 (33.3%) and three in group 2 (25%) and chorea in one patient in group 2 (4.2%).

The other major manifestations, subcutaneous nodules and erythema marginatum, were not observed. Increased ESR was the most common minor criterion occurring in 23 patients (95.8%). Fever, arthralgia, and positive CRP occurred in 19 (79.2%), 11 (45.8%), and 20 (83.3%) patients respectively. Table 4 shows that there is no significant statistical difference between the two groups of patients as regard major Jones' criteria (other than carditis) and minor Jones' criteria.

	Group (1)		Group (2)		P value
	n	%	n	%	
Major criteria					
• Arthritis	4	33.3	3	25	1.00 (ns)
• Chorea	0	0	1	4.2	1.00 (ns)
Minor criteria					
• Fever	9	75	10	83.3	1.00 (ns)
• Arthralgia	6	50	5	41.7	1.00 (ns)
• Increased ESR	11	91.7	12	100	1.00 (ns)
• Positive CRP	11	91.7	9	75	0.59 (ns)

Table 4: *Jones' criteria in the two groups.*

Fisher's Exact Test

Duration of treatment before remission ranged from 14 to 21 (16 ± 3.02) days. There was no significant statistical differences between the two groups of patients as regard the duration of treatment before remission, table 5. No complications related to steroids were observed in any of our patients. Table 5 also shows that there is no significant statistical difference between the two groups of patients as regard echocardiographic dimensions.

	Group 1	Group 2	P value
RVAW (mm)	4.5 ± 1.07	4.3 ± 1.13	0.71 (ns)
RV (mm)	9.08 ± 3.6	9.42 ± 3.6	0.71 (ns)
IVS (mm)	6.08 ± 1.6	5.7 ± 1.4	0.55 (ns)
LVEDD (mm)	40.79 ± 6.5	40.29 ± 6.7	0.76 (ns)
LVESD (mm)	25.71 ± 4.4	25.79 ± 4.38	0.93 (ns)
LVPW (mm)	4.8 ± 1.2	4.7 ± 1.3	0.80 (ns)
FS (%)	36.9 ± 5.3	35.3 ± 4.9	0.49 (ns)
Duration before remission in days	16.83 ± 3.19	16.42 ± 2.97	0.66 (ns)

Table 5*: Echocardiographic dimensions and duration before remission in the two groups of patients.*

Mann-Whitney test

Discussion

The incidence of both initial attacks and recurrences of ARF peaks in children 5 - 15 yr of age, the age of greatest risk tor GAS pharyngitis [4]. This coincides with our findings, where the ages of our patients ranged from 3.5 to 13 years (mean ± SD: 7.96 ± 3.29). Male to female ratio of our patients with acute rheumatic fever was 1 : 1.2. This is in accord with the known fact on RF that there is no sex predilection in its incidence [9].

Past history of recurrent acute tonsillitis or pharyngitis was positive in 70.83% of our patients. Considerable evidence supports the link between antecedent GAS upper respiratory tract infection and ARF and RHD. As many as two thirds of patients with an acute episode of RF have history of an upper respiratory tract infection several weeks before and the peak age and seasonal incidence of ARF closely parallel that of GAS pharyngitis.

Patients with ARF almost always have serologic evidence of a recent GAS infection. Their antibody titers are usually considerably higher than those seen in patients with uncomplicated GAS infections. Outbreaks of GAS pharyngitis in closed communities, such as boarding schools or military bases, may be followed by outbreaks of ARF. Antimicrobial therapy that eliminates group A streptococci from the pharynx also prevents initial episodes of ARF, and long-term, continuous antibiotic prophylaxis that prevents GAS pharyngitis also prevents recurrences of ARF [4]. Streptococcal pharyngitis might occur in a subclinical form or pass unnoticed until the discovery of RHD [10]. Certain studies have emphasized the relationship between the occurrence of RF and the severity of the clinical manifestations of the antecedent streptococcal pharyngitis [11]. While this is true in general, it is well documented that about one third of all cases of ARF follow mild, almost asymptomatic pharyngitis. It seems plausible that in populations that have ready access to medical care, the occurrence of severe pharyngitis would be associated with a lower incidence of RF because patients with more symptomatic pharyngitis are more apt to seek medical attention and receive treatment [12].

Family history of ARF or RHD was positive in 20.83%. Striking differences in the incidence of ARF and RHD among different ethnic groups are often evident within the same country; these differences are partially related to differences in socioeconomic status, and there is a genetic basis for increased susceptibility [4]. The relatively low attack rate of RF after untreated streptococcal pharyngitis (up to 2 to 3%) and the relatively high concordance of RF in monozygotic twins (19%) in comparison to dizygotic twins (2.5%) suggest the involvement of host genetic factors in susceptibility to RF. Several studies have suggested that genetic susceptibility to RF is linked to HLA class II alleles. However, there has been an apparent discrepancy as to the nature of susceptibility and/or protective alleles [13].

Among the 13 patients having recurrent ARF, only one was regular on LAP. Individuals who have already suffered an attack of ARF are particularly susceptible to recurrences of RF with any subsequent GAS upper respiratory tract infection. Therefore these patients should receive continuous antibiotic prophylaxis to prevent recurrences (secondary prevention). Secondary prevention is directed at preventing acute CAS pharyngitis. Secondary prevention requires continuous antibiotic prophylaxis, which should begin as soon as the diagnosis of ARF has been made and immediately after a full course of antibiotic therapy has been completed. The regimen of choice for secondary prevention is a single intramuscular injection of benzathine penicillin G (BPG) every four weeks. In certain high-risk patients, and in certain areas of the world where the incidence of RF is particularly high, use of BPG every three weeks may be necessary because serum concentrations of penicillin may decrease to marginally effective levels after three weeks. in US, the administration of BPG every three weeks is recommended only for those who have recurrent ARF despite adherence to a four-week regimen [4].

The present study cannot be used to verify the frequency of major Jones criteria in children with ARF in Egypt because we have selected the cases as, our goal was to compare single-dose with divided-dose steroids in treatment of rheumatic carditis however, the following observations could be elicited:

- Subcutaneous nodules and erythema marginatum did not occur in any of our patients.
- Among the 24 patients, only one had associated chorea (4.17%). This is similar to reports from developing countries where, the incidence of carditis in cases of chorea has often been between 10 and 15% [14].

No significant difference could be detected between the studied groups regarding shortening fraction. This is in agreement with Vasan and colleagues [15] who found similar results. Fractional shortening is preload, afterload, and heart rate dependent measure of myocardial contractility and that is why cannot be affected in active carditis unless severe enough to impair significantly the myocardial contractility [16].

Our results showed that there was no significant statistical difference between patients who received prednisolone as a single morning dose and those who received it in four-divided doses as regard the duration of treatment before remission. Moreover no complications related to steroids were observed in any of the two groups of patients. So our results show that prednisolone, as a single morning dose is as effective as divided doses for treatment of ARF with no higher risk of complications. As single-dose steroid therapy is convenient and likely to be associated with better drug compliance, we recommend it as the regimen of choice for treatment of ARF.

Elisabeth., *et al*. [17] found that during daily therapy, prednisone is as effective when administered as a single daily dose compared with divided doses. Our results are also in accord with results of Arvind and Mukta [18] who found that prednisolone, as a single morning dose was as effective as divided doses for inducing remission with no higher risk of gastrointestinal adverse effects.

A study from India failed to show any advantage of divided daily doses over single morning dosage in the time to remission, and an advantage of morning administration of steroids is that suppression of the pituitary-adrenal axis is minimized [19].

Complications related to corticosteroid toxicity (cushingoid appearance, hypertension, cataracts, and/or growth failure) did not occur in any of our patients. This indicates that giving steroids as a single morning dose is not associated with increased risk of complications related to steroids.

Conclusion

Prednisolone, as a single morning dose is as effective as divided doses for treatment of rheumatic carditis with no higher risk of complications. As single dose steroid therapy is likely to be associated with better drug compliance, we recommend it as the regimen of choice for treatment of rheumatic carditis.

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