Research Article

Underuse of Injectable Penicillin in Secondary Prophylaxis of Rheumatic Heart Disease in Nepal

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ABSTRACT

Background and Aims: Secondary prophylaxis have remained the mainstay of rheumatic fever and rheumatic heart disease management. Despite the proven efficacy and superiority of injectable penicillin in rheumatic heart disease patients, it has been underused in Nepal.

Materials and Methods: This is a hospital based cross-sectional study during June 2014 to October 2018 over a period of 52 months at College of Medical Sciences-Bharatpur including 350 patients with clinical and/or echocardiographic evidence of definite rheumatic heart disease. Data was collected from both cardiology outpatients and inpatients (admitted in cardioward/coronary care unit). Relevant data and information were entered into the pre-structured proforma and then analyzed by SPSS-16 software.

Results: The age of the patients ranged from 6 to 80 years with mean age 36.76±4.6years with female preponderance (F:M=1.26:1). The predominantly involved isolated valve was mitral in 152 patients (44.43%) followed by aortic valve in 70 patients (20.00%) and rest 90 (25.71%) had dual valvular involvement. The common complications encountered were heart failure in 200(57.14%) and arrhythmias in 155(44.29%) patients. Two hundred ten (60.00%) of the patients received penicillin (oral and injectable) and erythromycin. Majority 180/210=85.71%) were prescribed on oral penicillin whereas only 46/210=21.90% received injectable penicillin; the ratio being 3.35:1.

Conclusion: RHD is a leading cause of heart failure and death among young population. There is underuse of penicillin with very minimal focus on use of injectable penicillins currently. Hence, Nepal government and other non-governmental organizations should consider implementation of use of penicillin broadly and moreover focus on use and adherence of injectable penicillin.

Keywords: Rheumatic Heart Disease, Penicillin, Underuse, Secondary Prophylaxis.

Background

Rheumatic heart disease (RHD) is the most common cause of acquired heart disease in children and young adults globally and Nepal is not an exception to this. According to WHO, at least 15.6 million people worldwide have RHD [1] Of the 5,00,000 individuals who acquire acute rheumatic fever (ARF) every year, 3,00,000 go on to develop RHD and 2,33,000 deaths annually are attributable to ARF or RHD [1, 2]. Prevalence of RHD is even alarming in the young and adult population of rural South East Asian countries. Studies on RHD from different parts of Nepal in the last two decades have shown the prevalence to vary from 1.2 to 4.35 per thousand in school aged children [3-5].

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To tackle the burden of RHD, the World Heart Federation (WHF) released in 2013 a position statement on the prevention and control of RHD, with the ambitious goal of achieving a 25% reduction in premature deaths from ARF and RHD among individuals aged <25 years by 2025 [6].

RHD leads to early onset of heart failure in the young population along with multiple complications with lots of mortalities and morbidities each year. It also imparts huge economic and social burden in the Nepalese communities. Penicillin has been considered the treatment of choice for secondary prophylaxis of RHD. There is underuse and lack of adherence on use of injectable penicillin in Nepal. So, due consideration should be taken by the government on implementation of injectable penicillin usage strategies.

Aims and Objectives

This study is designed to study the use of penicillin in the secondary prophylaxis of rheumatic heart disease mainly focusing on underuse of injectable formulation.

Materials and Methods

This is a hospital based cross-sectional study during June 2014 to October 2018 over a period of 52 months at College of Medical Sciences-Bharatpur including 350 patients with 2D-echocardiography evidence of definite rheumatic heart disease.

Inclusion Criteria

Consecutive 350 patients with echocardiographic evidence of rheumatic heart disease from age 6 years and above were included in the present study.

2012 World Heart Federation criteria for the echocardiographic diagnosis of rheumatic heart disease was applied to reach the diagnosis [3].

Definite RHD (A, B, C, or D)

- A. Pathological MR and at least 2 morphological features of RHD of the MV

- B. MS mean gradient ≥4 mm Hg

- C. Pathological AR and at least 2 morphological features of RHD of the AV

- D. Borderline disease of both the AV and the MV

Exclusion Criteria

Those not fitting into the echocardiographic criteria for diagnosis of definite RHD and aged less than 6years were excluded from the study. Verbal consent was taken from each patient and patient party (if minority in age) during the study period. Data was regularly entered into the SPSS-16 software.

Statistical Analysis

The datas were analyzed by the statistician. Number and sex distribution were expressed in mean and standard deviation. P value of <0.05 was considered significant. Datas were collected from cardiology outpatients and inpatients. Relevant data and information were entered into the pre-structured proforma and then analyzed by SPSS-16 software. Ethical clearance was taken from the Local Ethical Committee of the hospital.

Observations and Results

The age of the patients ranged from 6 to 80 years with mean age 36.76±4.6years with female preponderance (F:M=1.26:1). In our study, patients with forty years or less were prescribed either oral penicillin, injectable penicillin, or erythromycin. Also, few people more than forty years with high risk of recurrent acute rheumatic fever and residing on high endemicity zone received secondary prophylaxis. Out of 350 patients enrolled in this study, only 210(60%) patients received penicillin and erythromycin therapy. Five of the patients had developed major penicillin reactions leading to its discontinuation and switching over to erythromycin therapy.

Majority of the patients in either group presented with shortness of breath, palpitation, chest pain, easy fatigability and swelling of the lower limbs with major overlapping of the symptoms. Mitral valve was the most involved valve in both groups followed by aortic valve. Diseased mitral and aortic valves were the most common combination lesions.

Heart failure (57.14%) was the most common complication followed by arrhythmias (44.28%) mostly atrial fibrillation in either groups (P<0.05). Eighteen (5.14%) patients expired during treatment due to decompensated heart failure.
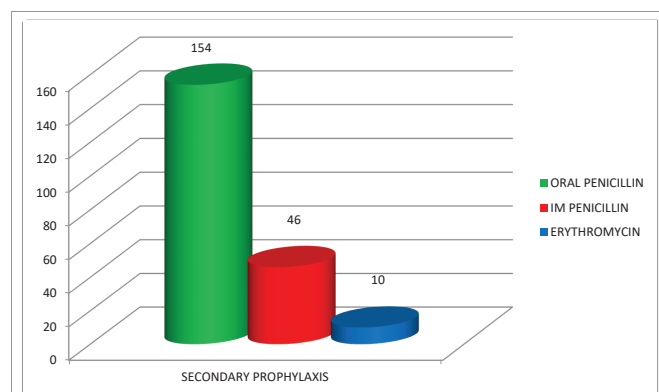

Figure 1: Bar diagram showing use of penicillin and erythromycin in RHD patients Out of patients receiving secondary drug prophylaxis, one hundred fifty four (73.33%) of the patients received oral penicillin while 46/210patients (21.90%) received intramuscular benzathine penicillin; the ratio being 3.35:1 as shown in bar diagram Figure 1.
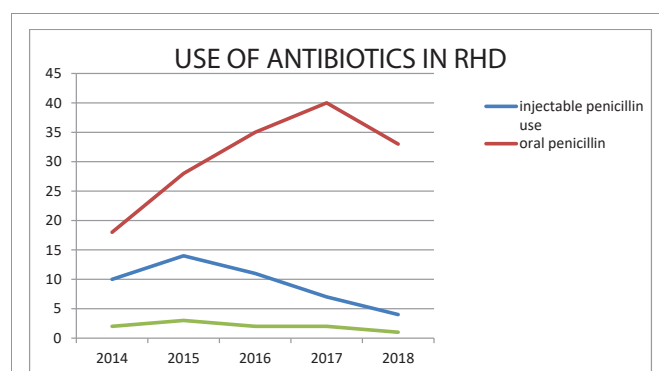

Figure 2: Trend of using different antibiotics in RHD the trend of using injectable penicillin has been surprisingly so declining in the recent years as shown above in Figure 2.

Discussion

Rheumatic heart disease (RHD) is characterized by immunological destruction of cardiac valves in the setting of episodes of acute rheumatic fever (ARF). ARF episodes occur after exposure to strains of the bacterium *Streptococcus pyogenes* (group A streptococcus [GAS]). The natural history of RF was markedly altered by the introduction of penicillin in the 1940s–1960s [7]. Secondary antibiotic prophylaxis has been shown to reduce of the risk of ARF recurrences and the development or worsening of RHD, with intramuscular benzathine penicillin G (BPG) having the most evidence for effectiveness [8, 9]. In the absence of recurrence, rheumatic carditis can naturally improve over several years.

In our study, the age of the patients ranged from 6 to 80 years with mean age 36.76±4.6years with female preponderance. The predominantly involved valve was mitral in 162 patients (46.28%) followed by aortic valve in 110 patients (31.43%). The common complications encountered were heart failure in 90(38.3%) and arrhythmias in 124(51%) patients. Similar findings were supported by Man Bahadur KC and Laudari et al [10, 11].

Out of 350 patients enrolled in this study, only 210(60%) patients received penicillin and erythromycin therapy. Out of patients receiving secondary drug prophylaxis, one hundred fifty four (73.33%) of the patients received oral penicillin while 46/210patients (21.90%) received intramuscular benzathine penicillin; the ratio being 3.35:1. Rest of the patients did not receive penicillin/erythomycin because of age >40 years and few defaulters. It was surprising to know that majority of the patients received oral penicillin.

Five of the patients in our study had developed major penicillin reactions leading to its discontinuation and switching over to erythromycin therapy. Our patients had major issues like-easy non-availability of the injectable drug, painful injection, noncompliance due to counseling by the doctor that they may develop anaphylaxis, attributing even minor reactions as unsafety during continuation on next time, unwillingness of the health manpower to administer it in the nearby centers and even fear among the health manpower especially the major drug reactions.

Till date, no primary preventive strategies for acute ARF are available in developing countries like Nepal and India. The only proven cost-effective intervention is secondary prophylaxis i.e., the long-term administration of antibiotics to people with a history of acute ARF or RHD, to prevent ARF recurrences and the development or deterioration of RHD. The best drug for this purpose is intramuscular benzathine penicillin G administered once every 3 weeks. They cite oral penicillin as a possible alternative but raise the concern of non-compliance to a daily routine over many years. For those allergic to penicillin, oral sulfadiazine or oral sulfasoxazole were considered optimal second choices. Oral erythromycin was reserved for those patients allergic to both penicillin and sulfa drugs [12].

Antibiotics used in secondary prophylaxis of RF from WHO Technical Report on RF and RHD 2004 [12].

Antibiotic	Mode of administration	Dose
Benzathine benzylpenicillin	Single IM injection every 3-4 weeks	≥30kg: 1.2 million units <30kg: 600,000 units
Penicillin V	Oral	250 mg twice daily
Sulfonamide (e.g. sulfadiazine, sulfasoxazole)	Oral	≥30kg: 1 gram daily <30kg: 500mg daily
Erythromycin	Oral	250mg twice daily

Four studies compared IM to oral penicillin. It appeared that IM penicillin was more effective in preventing RF recurrence, with all four studies showing a reduction in the risk of RF recurrence. In addition, there are supporting pharmacokinetic studies that have demonstrated that penicillin injections given IM every two or three weeks ensure serum penicillin levels remain above the minimum inhibitory concentration [13].

Techniques used to reduce the pain of benzathine penicillin injections include use of small gauze needles, increased injection volumes, addition of 1% lignocaine or procaine penicillin and

Table 1: Baseline characteristics of the patients (n=350).

Baseline parameters	Receiving penicillin/ erythromycin (n-210) Number	Percentage	Without penicillin (n-140) Number	Percentage	P value
Age					
<16years	35	16.67	0	0.00	0.04
16-30years	60	28.57	05	3.57	0.05
31-45years	95	45.24	15	10.71	0.03
46-60years	15	7.14	70	50.00	0.01
>60 years	05	2.40	50	35.71	0.02
Sex					
Male-	90	42.86	65	46.43	0.60
Female-	120	57.14	75	53.57	0.72
Clinical features					
-Shortness of breath	160	76.19	115	82.14	0.78
-Palpitation	80	38.09	66	47.14	0.65
-Chest pain	50	23.80	32	22.86	0.46
-Easy fatigability	110	52.38	85	60.71	0.52
Valvular involvement					
-Isolated mitral valve	92	43.81	60	42.86	0.86
-Isolated aortic valve	40	19.05	30	21.43	0.79
Combined lesions	55	26.19	35	25.00	0.95
-Mitral and aortic	15	7.14	10	7.14	0.84
-Mitral, aortic, and tricuspid					
Complications					
-Heart failure	115	54.76	85	60.71	0.51
-Arrhythmias	90	52.38	65	57.14	0.63
-Stroke	12	5.71	12	8.57	0.68
-Infective endocarditis	6	2.86	5	3.57	0.74
-Acute rheumatic fever	3	1.43	4	2.86	0.61
Outcome					
On follow-up	200	95.24	132	94.28	0.76
Expired	10	4.76	8	5.71	0.68

warming the medication to room temperature. Decisions about duration of secondary prophylaxis relate to the balance between the risk of recurrent ARF and the risk to the patient, should a recurrence occur (higher with increasingly severe heart disease) [14, 15]. The WHO report continues to suggest treatment for a patient without proven carditis for five years after the last attack or until 18 years of age (whichever longer). For a patient with carditis, ten years after the last attack or until 26 years of age (whichever longer). For those with more severe valvular disease or who have had valve surgery, prophylaxis should be lifelong [12].

Conclusions

There has been underuse of injectable penicillin as secondary prophylaxis in the recent years. The trend has been even declining in our study. The concerned authority needs to streamline the health care systems for long-term delivery of penicillin administration in challenging environments.

Conflict of Interest: The authors do not have any conflict of interests including finance in publication of this article.

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