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A retrospective observational study on drug-related problems in patients with rheumatic heart disease

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ABSTRACT

Rheumatic Heart Disease (RHD is one of the leading cause of public health degradation among children and adults since the twentieth century. Rheumatic fever mostly affects the population of developing countries, especially where poverty is widespread. About 2% of deaths worldwide due to cardiac failure is associated with RHD. Although pharmacotherapy in RHD is beneficial in its management, its outcomes may often be compromised due to the associated drug therapy problems (DTP). Data containing their demographic details, clinical presentation and drug chart was obtained and noted in a structured case report form. The data was compiled, and the drug-related problems associated with commonly prescribed drugs were evaluated. The prescription was critically analysed as per WHO guidelines for its appropriateness. The most commonly occurring DTP was potential drug interactions, sub-therapeutic dose, adverse drug reaction and drug duplication. Majority of the prescriptions were compliant to the recommendations of WHO guidelines. The study highlights the potential drug-related problems in the management of RHD and hence indicates that there is still room to improve rational prescribing for patients with RHD. Rheumatic Heart Disease, drug-related problems, drug interactions, adverse drug reactions, drug duplication, overdosage, Rheumatic fever.

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INTRODUCTION

Rheumatic Heart Disease, a non-suppurative complication of Group A streptococcal streptococci, had been identified to be one of the leading causes of public health degradation among children and adults since the 20th century, especially in the rural, semi-urban and also some parts of the urban areas (WHO Technical Report Series., 2001, No. 923). Although the incidence and prevalence of rheumatic heart disease have reduced substantially in a decade, it continues to be a study of concern mainly among the impoverished, undernourished and overcrowded population. About 2% of deaths worldwide due to cardiac failure is associated with rheumatic heart disease (WHO factsheet on cardiovascular diseases., 2017). In India, the prevalence of rheumatic heart disease has reduced to less than 2% from 35% in two decades (Meenakshisundaram, R. and Thirumalaikolundusubramanian, P., 2009).

Rheumatic heart disease is a chronic heart condition characterised by poor functional capacity of heart due to inflammatory changes and scarring of myocardium and other cardiac valves (Blix HS *et al*., 2004 and He VYF *et al*., 2016). It occurs when the antibodies produced by the body wrongly attacks its tissue due to antigenic mimicry. Most patients diagnosed with chronic rheumatic heart disease were also analysed to have multi-valvular

comorbidities such as mitral stenosis, mitral regurgitation, aortic stenosis, aortic regurgitation, tricuspid stenosis, tricuspid regurgitation and pulmonary arterial hypertension (Kevin H *et al*., 2016).

Although pharmacotherapy in rheumatic heart disease is beneficial in its management, its outcomes may often be compromised due to the associated drug therapy problems (Carole P.K *et al*., 2015 and Hassell TA *et al*., 1972). A drug-related problem (DRP) is an event involving drug treatment which interferes with the patient achieving an optimum outcome of medical care. A DRP may occur at any stage of the therapy from prescription to follow-up procedure. They occur most frequently in inpatients leading to increased morbidity, mortality, extended hospital stays and unnecessary expenditure of the patients, affecting their quality of life (Urbina O *et al*., 2015 and Tegegne GT *et al*., 2014). The most commonly occurring DRPs include:

1. Adverse Drug Reactions: They are any unwanted effects produced by the prescribed medication.
2. Drug Interactions: They are undesirable effects caused due to the interaction between the prescribed drugs or drug and food.
3. Non-Compliance: It is when the patient fails to take the prescribed medication due to pharmaceutical, sociological or economic reasons.
4. Over Dosage: The patient is prescribed a dose more than that required to treat the condition.
5. Sub-Therapeutic Dose: The patient is prescribed a dose lower than that required to produce an essential pharmacological effect.
6. No Medical Indication: The patient has prescribed a drug for which there is no clinical indication.
7. Drug Duplication: The patient is prescribed multiple drugs for the same indication.

Drug-related problems may impose a serious threat to the therapeutic efficacy and safety in patients with rheumatic heart disease (Mendis S *et al*., 2011). Increased number of medications, complex drug regimens, availability of new drug therapies, multiple dosage forms for a single medication and lack of adherence to standard treatment protocols increase the potential for drug-related problems. Cardiovascular drugs used in the treatment of RHD have an increased risk of producing DRPs (Andreazza RS *et al*., 2011 and Abraham RR and Devi ASM *et al*., 2012).

Early identification of the potential and actual drug-related problems are beneficial in reducing mortality, improving patient's quality of life and also optimising healthcare costs. Awareness about drugs prone to cause DRPs helps to use them more cautiously to prevent any possibility of adverse events and hence enhance the efficacy and safety of pharmacotherapy (Shareef J *et al*., 2014). Hence the study identifies and categorises the drug-related problems associated with the therapy of RHD so that the physician along with the pharmacist may construct a better healthcare plan and also for its prevention and management in future. Generally, the result will be beneficial in clinical practice.

METHOD

About 112 patients with RHD were enrolled into the study as per the inclusion and exclusion criteria, and case report forms were used to collect the required data such as the patient demographic data, clinical presentation while admission, comorbidities present, clinical and biochemical data pertaining to RHD and prescribing pattern of drugs in such patients. All the prescriptions were analysed clinically.

The appropriateness of the drug therapy was assessed as per the recommendations of the WHO guidelines for RHD.

The data were compiled in Microsoft Excel sheet and the mean, median and standard deviation of age, no. of drugs and no. of DRPs encountered per prescription were calculated. The results were interpreted with the help of tables and graphs.

RESULTS

Around 258 patient case sheets were screened, and only 112 were enrolled in the study based on the inclusion and exclusion criteria. A total of 112 patient's case report forms were identified and subjected to data collection in order to analyse for any potential drug related problem. The mean (±SD) age of the study population was 42.75±10.3 (Median-43, range 19-64) with a surprisingly equal number of males and females. The incidence of RHD was most commonly observed in the age group of 19-30 years, i.e. in the young adults, with no significant variation among gender. Most of the patients suffering from rheumatic heart disease were found to be anaemic (65.18%), and some of them had complaints of inadequate sleep due to dyspnoea (11.61%). About 39.29% patients were associated with other comorbidities of which majority (30.36%) of them had endocrine disorders and other cardiovascular diseases like diabetes mellitus, hypertension, dyslipidemia, coronary artery disease and thromboembolism. Very few patients were known to have lung disorders and gastritis.

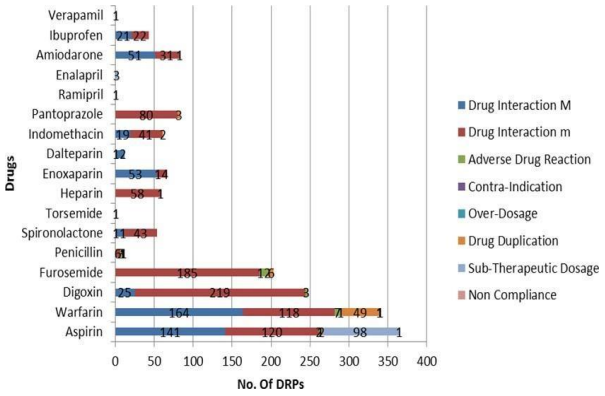

Table 1: Category Wise Distribution of DRPs

S.No	DRPs	No. of DRPs
1	Drug Interaction	
	Major	353
	Moderate	750
2	Adverse Drug Reaction	32
3	Drug Duplication	70
4	Non Compliance	2
5	No Medical Indication	6
6	Contra-Indication	2
7	Over-Dosage	1
8	Sub-Therapeutic Dosage	105
Total		1321

Table 2: ADR Wise Distribution

Drug	Adr	No. Of patients
Aspirin	Gi bleeding	2
Warfarin	Bleeding	7
Digoxin	Digitalis toxicity	3
Furosemide	Hypokalemia	12
Penicillin	Rashes	3
Torsemide	Hypokalemia	1

The study involved patients suffering from rheumatic heart disease for as long as 0-35 years, where about 44(39.29%) patients were cases of newly detected RHD. The remaining cases included patients already suffering from RHD and on treatment. The study showed that the incidence of rheumatic heart disease is more common during childhood and young adult and is associated with chronic multivalvular comorbidities in the later years. The risk of multi-valvular diseases associated with RHD was found to be higher in adults aged 19-40 years. Most of the patients showed abnormal clinical features in echocardiography, ECG and chest x-ray with left atrial enlargement taking the highest toll followed by left ventricular hypertrophy and left ventricular enlargement. Other characteristics observed were right atrial enlargement, right ventricular enlargement, right ventricular hypertrophy and left atrial clot. Out of the 112 patients observed, 109 patients had undergone surgery, of which 64(57.14%) patients had undergone mitral valve replacement, 33(29.46%) patients underwent double valve replacement, and 11(9.82%) patients underwent aortic valve replacement. Few patients had also undergone tricuspid valve repair or annuloplasty.

Almost all the patients were diagnosed with other chronic valvular diseases associated with rheumatic heart disease. About 40.18% patients were found to have multi-valvular heart disease with pulmonary arterial hypertension, 23.21% patients were diagnosed with mixed mitral valve disease with pulmonary arterial hypertension, 8.04% patients reported mixed mitral valve disease alone, and 7.14% patients showed multi-valvular heart disease. Very few patients were observed to have pure mitral stenosis (3.57%), mitral regurgitation (0.89%) and aortic stenosis (0.89%) comorbid to rheumatic heart disease.

The major reason for admission was dyspnoea on exertion (93.75%) - grade 2 and 3 taking the highest toll, paroxysmal nocturnal dyspnoea (26.79%), palpitation (30.36%), chest pain or angina on exertion (26.79%) and orthopnoea (20.54%). Only 7 patients had complaints of rheumatic joint pain, and 12 patients had a known past history of rheumatic fever.

A total of 1750 drugs were administered to 112 patients with RHD. The most commonly prescribed drug category included antimicrobials (18.23%), followed by anticoagulants (12.63%), diuretics (11.77%) and adjuvant supplements (10.11%). Other drug categories prescribed were ACE inhibitors, ARB blockers, antiplatelet agents, calcium channel blockers (CCBs), cardiac glycosides, antidyslipidemics, antiarrhythmics, hypoglycemic agents, NSAIDs, analgesics, proton pump inhibitors (PPIs), antihistamines, bronchodilators and expectorants. The mean (±SD) number of drugs per encounter was found to be 15.63±4.83. Commonly prescribed drugs included- ionotropic agent digoxin (100%), antiplatelet agent like aspirin (97.27%), CCB verapamil (81.25%), antiarrhythmic amiodarone (78%), proton pump inhibitor ranitidine (73.43%), antidyslipidemic atorvastatin (69.23%), ACE inhibitor enalapril, phenoxymethylpenicillin secondary prophylaxis (57.78%), furosemide diuretic (49.51%), anticoagulant warfarin (46.61%), β-blockers atenolol and metoprolol (43.34%) and ARB blocker losartan (42.86%).

Around 1321 DRPs were observed in 112 patients, and the mean (±SD) number of drug-related problems was found to be 11.79±5.29. Drug interactions (major & moderate), sub-therapeutic dosage, drug duplication and adverse drug reaction were the most commonly seen DRPs (Table 1). Most of the DRP was found to be associated with aspirin, warfarin and digoxin. Contraindication was observed in 2 patients on aspirin and penicillin. Non-

Table 3: Commonly Observed Major Drug Interaction

S.No	Drug interactions	No, of patients	Percentage (%)	Effect
1	Warfarin+Aspirin	94	7.12	Increased risk of bleeding
2	Ofloxacin+Warfarin	5	0.38	Increased risk of bleeding
3	Ibuprofen+Warfarin	10	0.76	Increased risk of bleeding
4	Ibuprofen+Aspirin	11	0.83	Decreased antiplatelet effect of aspirin, the additive risk of bleeding
5	KCl+Spironolactone	11	0.83	Hyperkalemia
6	Warfarin+Indomethacin	13	0.98	Increased risk of bleeding
7	Warfarin+Enoxaparin	24	1.82	Increased risk of bleeding
8	Amiodarone+Digoxin	25	1.89	Digoxin toxicity
9	Amiodarone+Warfarin	26	1.97	Increased risk of bleeding
10	Warfarin+Dalteparin	5	0.38	Increased risk of bleeding
11	Enoaxaparin+Indomethacin	6	0.45	Increased risk of bleeding

compliance was studied in 2 patients; the reason is an unwillingness to take the drug and forgetfulness. The wise drug distribution of the DRPs is shown in Figure 1. The most commonly observed ADR was hypokalemia associated with loop diuretics. Gastro-intestinal bleeding was observed in some patients taking aspirin and warfarin. Digitalis toxicity associated with digoxin was observed in 3 patients (Table 2). Commonly encountered potential major interactions are listed in Table 3.

No statistically significant difference was found between males and females with regard to the occurrence of drug-related problems. All male study participants encountered a potential major drug interaction whereas only 4 female patients did not have any potential major drug interaction. All the prescriptions were critically analysed against the recommendations of WHO treatment guidelines in the management of RHD, and it was observed that 83.03% of them were compliant to those recommendations. About 16.96% of prescription was deviating from the recommended guidelines in the treatment of RHD.

DISCUSSION

RHD is one of a leading non-communicable disease that requires secondary prophylaxis with long-acting penicillin to prevent the recurrence of ARF, and oral anticoagulants with rheumatic atrial fibrillation. Studies have reported that anticoagulants highly interact with concomitantly administered drugs, therefore increasing the chances for a DRP (Bland, E.F. and Jones, D. 1951). This study aimed at exploring the DRPs associated with RHD patients retrospectively.

The median age (43 years) of the study population was found to be higher than that reported by Zuhlke, L *et al*., 2015 (Zuhlkel L *et al*., 2015). This may be because the study included patients with a past medical history of RHD and the duration of RHD in the study population was 1 to 35 years. A majority of the patients had valvular diseases associated with RHD which is in line with that reported by Zuhlke, L *et al.*, 2015.

The mean number of drugs per prescription was found to be higher than that reported by the WHO (1.3 to 2.2). Hence, we can say that the prescription was irrational. The main reason for this could be the practice of polypharmacy and also the increas- ing complexity of the drug regimens (Meenak- shisundaram, R. and Thirumalaikolundusubrama- nian, P., 2009). The most commonly prescribed drugs for the treatment of RHD were observed to be aspirin, warfarin, digoxin, furosemide, enalapril, losartan, metoprolol, ranitidine, atorvastatin, pen- icillin, verapamil, amiodarone and ibuprofen.

The mean DRP encountered per prescription was 11.79, which is highest than ever reported and is alarming. The most common DRP observed were potential interactions of the type both major and moderate. However, the pharmacological effects of those potential DIs were monitored as recommended in most of the patients. Other studies involving CVD patients have reported indication - need additional drug therapy, efficacy and safety-related DTP (Shareef, J *et al*., 2014), and unnecessary drug therapy as one of the most common DTP in their study.

The second common DTP type was found to be drug duplication in the current study followed by ADR. About 13 patients were observed to have hypokalemia of which 12 of them were associated with furosemide and 1 with torsemide. About 9 patients had reported GI bleeding of which 7 cases were associated with Warfarin and 2 with Aspirin. Other adverse reactions reported included digitalis toxicity with digoxin in 3 patients and rashes with penicillin in other 3 patients. The study also reports that most of the prescription were criti-

cally analysed to be appropriate as per the recommendations of the WHO guidelines for management of RHD.

CONCLUSION

The study highlights the potential drug-related problems in patients with RHD. The most common DRP observed were potential drug interactions and drug duplication. The results indicate that there is still room to improve in rational prescribing for patients with RHD.

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