COLLEGE OF HEALTH SCIENCES
SCHOOL OF MEDICINE
DEPARTMENT OF PEDIATRIC AND CHILD HEALTH

PREVALENCE OF BENZATHINE PENICILLINE ADVERSE REACTION IN PATIENTS WITH RHEUMATIC HEART DISEASE TAKING MONTHLY BENZATHINE PENICILLINE ADDIS ABABA ETHOPIA

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A RESEARCH THESIS SUBMITTED TO DEPARTMENT OF PEDIATRICS AND CHILD HEALTH, SCHOOL OF MEDICINE, COLLEGE OF HEALTH SCIENCES, ADDIS ABABA UNIVERSITY FOR THE PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE CERTIFICATE IN PEDIATRICS AND CHILD HEALTH.

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Prevalence of benzanthine penicillin adverse reaction in patients with Rheumatic heart disease taking monthly benzanthine penicillin injection:a cross-sectional survey

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A research thesis to be submitted to Addis Ababa University, College of Health Science, Department of Pediatrics and Child health as a fulfillment for completion of Residency program.

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Declaration

I, the undersigned, Pediatrics and Child Health final year resident, declare that this thesis done is my original work in partial fulfillment for the certificate of Pediatrics and Child Health.

Title: - Prevalence of benzanthine penicillin adverse reaction in patients with Rheumatic heart disease taking monthly benzanthine penicillin injection:

Submitted by;

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Name of Resident **.....**

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Date

Approved by;

Advisor.

Dr. Tamrat Moges **_____**

Signature **_____ Date**

Acknowledgment

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List of Abbreviations and Acronyms

1. ARF:-Acute Rheumatic Fever
2. GAS:-Group A Streptococcus
3. RHD:-Rheumatic Heart Disease
4. BPG:-BenzanthinePenicillin G
5. SAP:- Secondary Antibiotic Prophylaxis
6. RF:- Rheumatic Fever
7. WHO:- World Health Organization
8. TASH:-TikurAnbessaSpecializedHospital
9. CRVHD :- chronic rheumatic valvular heart disease

Abstract

Background: Rheumatic Heart disease (RHD) is by far the most important form of acquired heart disease in children and young adults and continues to be a health problem living in many low and middle-income countries and especially in sub-Saharan Africa. Several strategies have been implemented for rheumatic fever and RHD control. These include primary, primordial and secondary prevention. Benzathine penicillin G (BPG) secondary antibiotic prophylaxis (SAP) has been shown to reduce the risk of ARF recurrences and the development or worsening of RHD with well-established effectiveness. Despite BPG favorable safety profile, a few severe adverse events have been reported and these serious adverse reactions can have a devastating effect on RHD control programs.

Objective: This study was aimed at assessing the magnitude of the problem of adverse drug reaction due to benzantine penicillin and its contributing factor

Method: A retrospective cross-sectional study was done among pediatric and adult patients who are diagnosed to have CRVHD(chronic rheumatic valvular heart disease) and on follow-up at pediatric and cardiac clinic respectively and taking monthly benzathine penicillin who came for follow-up from December 2020. to October 2021. The data were entered and analyzed by using SPSS version 25. Data collection was conducted exclusively by the principal investigator through telephone interview.Descriptive statistics were employed to summarize the data, and data were presented using Tables and Figures. Binary logistic regression analysis was done to assess predicting factors associated with benzathine penicillin adverse reaction. A p-value <0.05 was considered as statistically significant.

Result: A total of 460 pediatric and adult patients who fulfilled the inclusion criteria were enrolled. The prevalence of benzathine penicilline adverse reaction is 21%. The strength of association of both dependent and independent variables was assessed using odds ratio and 95%CI. Accordingly, participants whose age is in the range of 15-18 years had 3.2 fold increased risk to develop benzathine penicillin adverse reaction (AOR=3.2, 95%CI=1.07, 18.62) and age range of 18-30 years had 9.2 fold times increased risk to develop adverse drug reaction when compared to age range of 5-14 years.

Conclusion: In this study, Adverse drug reaction of benzanthine penicillin G is common. Factors which are significantly associated with high rate of adverse reaction are age range of 15-30,female sex and self and family history of allergy.

1. **INTRODUCTION**

1.1. Background

Acute rheumatic fever (ARF) is a nonsuppurative complication of pharyngeal infection with group A *Streptococcus* (GAS). The clinical presentation includes arthritis, carditis, chorea, subcutaneous nodules, and erythema marginatum. It is frequently associated with significant heart valve damage, termed rheumatic heart disease (RHD)(1).

RHD stems from an abnormal immune reaction to group A streptococcal infection (GAS), precipitating acute rheumatic fever (ARF). Repeated GAS infections cause recurrent ARF episodes in susceptible individuals. These recurrent episodes induce irreversible heart valve damage known as rheumatic heart disease. RHD significantly increases mortality owing to increased incidence of heart failure, arrhythmias, stroke, endocarditis(2).

Worldwide, 33 million people live with rheumatic heart disease (RHD), the vast majority in developing countries according to the global, regional and national burden of RHD 2017 data(3) and In Ethiopia, a study done in rural areas 2017 shows the prevalence of RHD is 37.5 cases per 1000 population(4). The remainder of people with RHD lives in vulnerable or indigenous communities worldwide.

The annual incidence of acute rheumatic fever in some developing countries exceeds 50 per 100,000 children, and very high rates are also seen in ethnic minority populations within Australia and New Zealand(5). Worldwide, rheumatic heart disease remains the most common form of acquired heart disease in all age groups, accounting for as much as 50% of all cardiovascular disease and as much as 50% of all cardiac admissions in many developing countries. Striking differences in the incidence of acute rheumatic fever and rheumatic heart disease among different ethnic groups are often evident within the same country; these differences are partially related to differences in socio-economic status, and there is a genetic basis for increased susceptibility(5).

The burden of ARF and RHD are major public health problems in low-income countries(6). The prevalence of RHD appears to be increasing worldwide and it remains a significant cause of cardiovascular morbidity and mortality(7).In high-income countries, RHDs have been eliminated and are not public health problems, while it continues to cause significant morbidity and premature mortality in low-income settings as overcrowding and low socio-economic status are the known risk factors for the occurrence of ARF(8).

Several strategies have been implemented for rheumatic fever and RHD control. These include primary, primordial and secondary prevention(9). Though primary preventions of ARF in those individuals at risk of developing the disease condition are considered a cornerstone in RHD management(10), secondary prevention remains the widely practiced management approach in the care of individuals once they develop RHD(11,12). Benzathine penicillin G (BPG) secondary

antibiotic prophylaxis (SAP) has been shown to reduce the risk of ARF recurrences and the development or worsening of RHD with well-established effectiveness(5).

BPG is formed by the addition of benzathin ecounterion to penicillin sodium, creating a molecule with poor aqueous solubility. Intramuscular injections of BPG provide protracted serum penicillin concentration detectable for weeks(13,14). This 'slow release' profile means that BPG can be administered every 2, 3 or 4 weeks to people with a history of ARF to reduce the risk of recurrent GAS infections and ARF episodes. At high levels of adherence, this secondary prophylaxis strategy reduces RHD progression and severity(15). Prophylaxis with oral alternatives was found to be less effective at preventing ARF recurrences in all four relevant studies identified in a 2013 systematic review. Three of these studies also found that oral alternatives were less effective at preventing streptococcal throat infections(16). On this basis, the 2010 American Heart Association guidelines for secondary prophylaxis identification provides a grade 1A recommendation for four times a week intramuscular BPG relative to oral penicillin given two times a day, which is a grade 1B recommendation(17). Secondary prophylaxis is widely recommended for ten years after the first episode of ARF(17).

Despite BPG favorable safety profile, a few severe adverse events have been reported since it was first marketed in 1954. The well-known adverse event of BPG administration is related to the risk of immediate-type hypersensitivity reactions to penicillin manifesting as anaphylactic shock and possibly death(18). However, less familiar non-allergic reactions have also been described. The most likely pathophysiologic explanation for these fatalities is that the BPG compound is a crystal powder that may cause direct damage when injected into a blood vessel, possibly eliciting vascular spasm and subsequent occlusion by the large crystal of the penicillin salt(19).

Table 1 Diagnostic Criteria for Anaphylaxis

Anaphylaxis is highly likely when any one of the following three criteria is fulfilled
1. acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue or both, e.g., generalized hives, pruritis or flushing, swollen lips-tongue-uvula)
And at least one of the following
A. Respiratory compromise (eg.dyspnea,wheeze-bronchospasm,stridor hypoxemia_
Reduced BP or associated symptoms of end-organ dysfunction) eg,hypotonia,collapse,syncope,incontinence)

2. Two or more of the following that occurs rapidly after exposure to a likely allergen for the patient (minutes to several hours)
A.involvement of the skin mucosal tissue (e.g., generalized hives,itch-flush, swollen lips-tongue-uvula)
B.Respiratory compromise (eg,dyspnea,wheeze-bronchospasm,stridor,hypoxemia)

C.Reduced BP or associated symptoms (eg,crampy abdominal pain, vomiting)

3. Reduced BP after exposure to a known allergen for that patient (minutes to several hours)
A.infants and children –low systolic BP(age-specific) or greater than 30% decrease in systolic BP. B.adults-systolic BP of less than 90mmhg or greater than 30% decrease from that person's baseline

Table 2 Brighton criteria for anaphylaxis

Organ system	Major criteria	Minor criteria
Dermatological or mucosal	➢ Generalized urticarial(hives)or generalized erythema ➢ Angioedema (not hereditary), localized or generalized ➢ Generalized pruritus with skin rash	➢ Generalized pruritus without skin rash ➢ Generalized prickle sensation ➢ Localized injection site urticarial ➢ Red and itchy eyes
Cardiovascular	➢ Measured hypotension ➢ Clinical diagnosis of uncompensated shock indicated by at least three of the following - tachycardia, capillary refill >3 second reduced central pulse volume decreased level or loss of consciousness	➢ Reduced peripheral circulation as indicated by the combination of at least two of the following tachycardia capillary refill time of >3second without hypotension a decreased level of consciousness
Respiratory	➢ Bilateral wheeze(bronchospasm) ➢ Stridor ➢ upper airway swelling (lip,tounge,throat,uvula or larynx) ➢ respiratory distress,	➢ persistent dry cough ➢ hoarse voice difficulty breathing without wheeze or stridor ➢ sensation of throat closure ➢ sneezing

	defined by two or more of the following Tachypnea increased use of respiratory muscle recession Cyanosis Grunting	,rhinorrhea
Gastrointestinal		➢ Diarrhea ➢ Abdominal pain nausea ➢ Vomiting
Laboratory		Mast cell tryptase elevation >upper normal limit

Anecdotal reports of adverse reactions to BPG have been commonly heard at cardiology conferences for several years, highlighting clinician concern over perceived quality issues(20). In 2013, the World Heart Federation surveyed 39 clinicians prescribing BPG: 20% reported having a patient die from anaphylaxis, and 26% knew of a case of anaphylaxis to BPG causing death(24).

Serious adverse reactions can have a devastating effect on RHD control programs. Historically, health workers fear of anaphylaxis was found to be one of the major reasons for discontinuation of BPG prophylaxis.(22) Some states in India have banned BPG injections, given concerns about adverse reactions (14). In Israel, BPG products have been withdrawn, and physicians advised to use alternative medications(23). Understanding and addressing these events is imperative to realize the disease-altering benefits of secondary prophylaxis for people living with RHD. Therefore this study is conducted to assess the prevalence of adverse reactions of benzathine penicillin.

1.2 Statement of the problem

benzathine penicillin is one of the drugs which is used for secondary prevention of rheumatic heart disease .there are anecdotal reports of different adverse reactions of benzanthine penicillin(20) and this serious adverse reaction can have a devastating effect on RHD control. But the prevalence of these adverse effects are not well studied and contemporary data about the prevalence of penicillin allergy are difficult to collect given penicillin allergy is widely over-reported(25)

In a study done at TikurAnbessa hospital on adherence to benzantine penicillin 2017, it was found that one of the common reasons to miss the monthly benzantine penicillin is the unwillingness of healthcare professionals to administer the drug because of fear of its side effects(26). Also, in a study done in Zambia, a great majority of participants had grave fear of inducing adverse reactions based on anecdotal information(27). So it is important to know the prevalence and associated risk factors of adverse reaction of BPG and its impact.

1.3 Significance of the study

Despite few studies done on the adverse effect of benzanthine penicillne, to my knowledge, there are no studies done in our country. Hence, this study is the first study in TASH and will help us to know the prevalence of adverse reactions of benzanthine penicilline in those who are taking it on a monthly basis, will try to identify the common symptom of those adverse reactions and will identify its impact on the follow-up .this will help in general to have a better understanding of the adverse drug reaction and improve the overall care of the patient. Also, the finding of this study can serve as baseline data and help another investigator as a reference for future studies.

2. LITERATURE REVIEW

2.1 Prevalence of adverse reaction of benzathine penicilline

There are few previous studies done on the adverse reaction of BPG.the first study is done in Western Australia in 2019, Nineteen reports were identified describing adverse events following BPG administration. Twelve reports pertained to patients receiving BPG for RHD prophylaxis and seven patients receiving BPG for other indications. A report of adverse reaction to BPG was also identified from pharmacovigilance activities in Zimbabwe. These are reported chronologically to illustrate the changing pattern of adverse reactions over time.

In 1958, Hsu and Evans reported a cohort study including systemic adverse reactions in 6 of 32 adults with RHD. The majority of these were cutaneous reactions. One serious, systemic adverse reaction was reported in a 54-year-old woman with advanced valvular RHD. After 18 months of regular BPG injections, the patient collapsed within minutes of routine BPG administration and died(29).

Steigmann and Suker in 1962 outlined a case series of three fatalities attributed to anaphylactic shock following BPG administration: a 19-year-old man, a 49-year-old man and a woman of unspecified age(19). All three patients had RHD with either known cardiac complications or cardiomegaly at autopsy. In 1976, Lu e*t al.* reported seven allergic reactions (one delayed type reaction, four serum sickness reactions and two anaphylactic reactions) in 105 patients with ARF or RHD(22). Demographics and outcomes for the patients who suffered anaphylactic reactions were not reported.

The only large-scale study to date was a prospective study carried out in 1991 by the International Rheumatic Fever Study Group(30). A total of 1790 patients were enrolled over 1988–1990, an equivalent period of 2736 patient years. A total of 32 430 injections were given. Allergic reaction following BPG administration was reported in 57 of 1790 patients. Four episodes of anaphylactic reactions occurred; three of these people recorded as having anaphylaxis were being actively treated for cardiac failure. Three recovered and one died: a 15-year-old girl with severe mitral valve disease and chronic congestive cardiac failure who died 6 days after injection. From this study, the rate of allergic reaction to BPG was estimated at 3.2%, with anaphylaxis estimated at 0.2%. The frequency of anaphylactic reaction was calculated at 1.23 per 10 000 injections(18). Also in a study done in nepal the incidenceof allergic reaction was 1.4%.

2.2 Associated risk factor for the adverse reaction

In the above reports, there are four hypothesis given as an explanation for the possible cause of severe adverse reaction or death. The first is anaphylaxis; in all cases, the adverse event occurred within 1 hour of BPG administration, consistent with the core definition of anaphylaxis as having

‘rapid onset’(31). A number of cases had evidence of cardiovascular and respiratory compromise; however, only three of the cases reported dermatological symptoms, which are needed to meet Level 1 Brighton criteria for anaphylaxis(31).

The second hypothesis is the problem with BPG products, in which all adverse reactions occurred after the powdered form. More recent studies have shown that different brands of powdered BPG have altered physical characteristics including crystal shape and differences in solubility, both affecting the rates of needle blockage(32,33).

The third hypothesis is the injection technique in which inadvertent intravascular and intra-arterial administration of BPG could cause collapse and sudden death because of the formation of emboli after injection. Also, injection in the dorsoglutealregion may cause vascular damage(34). In 2 of these 10 cases, local anesthetic lignocaine was added to diluents prior to administration. This is intended to reduce the pain of administration and is standard practice in some settings(35).

The fourth hypothesis is that the underlying structural cardiac disease itself predisposes to adverse outcomes. Severe valvular disease contributes to severe adverse reactions and death n particular. It is well established that mitral valve disease is a risk factor for arrhythmias and sudden cardiac death. Vasovagal hypotension/syncope, a well-described response to intramuscular injection, could also contribute, particularly in patients with severe valvular disease resulting in inadequate compensatory mechanisms.

From a study done in Israel and Switzerland in November 2017 on fatal and near-fatal non-adverse reactions in patients with cardiac disease receiving BPG, the study shows fatal non-allergic reaction which occurs in both adults and children after intramuscular administration and the reaction occurs as quickly as a few minutes following administration(37). There were nine case series and from this, hypersensitivity reactions were not seen in all cases. Furthermore, in the vast majority (8/9), the patients had been repeatedly exposed to BPG prior to the adverse event or death(37).

3. OBJECTIVES

3.1 General objective

- To determine the magnitude of the problem of adverse drug reaction due to benzantine penicillin based on caretakers and patient reports among patients who have followed up at TASH for RF/RHD.

3.2 Specific objectives

- To identify the most common symptom of those adverse reactions,
- To identify contributing factors for the development of the adverse reaction.
- To identify the impact it had on the follow-up.

4. METHODS AND MATERIALS

4.1.Study Area

This study was conducted in Addis Ababa, Ethiopia, at TikurAnbessa Specialized Hospital. The hospital is found in the capital city of Addis Ababa in the Lideta sub-city. The hospital opened in 1972, and is a very large referral hospital and is one of the largest teaching hospitals in the country, providing undergraduate as well as post-graduate teaching services. It is also an institution where specialized clinical services are being given; out of them are a pediatric and adult cardiac clinic that works five times per week staffed with residents, nurses and cardiologists.

4.2.Study Period

This study was conducted from December 2020 to October 2021 on patients who were diagnosed to have RHD and who came for follow up at both pediatric and adult cardiac clinics who came for follow-up from July 1, 2020 to July 25, 2021 (patients who had follow-up for the past one year from the last study period).

4.3.Study Design

Hospital-based cross-sectional descriptive study that involved interviewing patients or their guardians(for the pediatrics) who have follow up at TASH for RF/RHD was conducted regarding the adverse effect of benzantine penicillin injection. The data collection questioner was developed from different literature and was modified based on the local context. The questioner was prepared in English and was translated into Amharic.

4.4. Population

Source Population: All pediatric and adult patients with RF/RHD on monthly BPG injection who came for follow-up at the pediatric and adult cardiac clinic of TASH.

Study population: All patients who have Rheumatic fever and RHD on follow-up who fulfill the inclusion criteria and are willing to be interviewed and who were on monthly benzanthine penicillin injection within the study period.

4.5.Inclusion and Exclusion criteria

- Inclusion criteria: All pediatric and adult RHD patients who were on monthly benzanthine penicillin having follow-up at TASH and are volunteers for telephone interview.

- Exclusion criteria: those who didn't pick their telephone with a two-time trial, and those who were not willing for the telephone interview were excluded.

4.6. Sample size determination

The assumptions used to calculate the actual sample size are; 95% level of confidence with 0.05 α value (which yields $Z\ \alpha/2 = 1.96$ on the standard normal distribution curve), 5% margin of error. With these assumptions using a single population proportion formula:

$$n = \frac{\left(Z\frac{\alpha}{2}\right)^2 p(1-p)}{d^2}$$

Where n = is a sample size
z = the value of the standard normal curve score corresponding to the given
Confidence interval = **1.96**
p = estimated proportion of patients who are on regular monthly benzanthine penicillin and develop the reaction.
d = the permissible margin of error (the required precision) = 5%

$$n = \frac{(1.96^2)(0.50(1-0.50))}{0.05^2} = 384$$

n=384
After adding 20% non response rate =460

4.7.Study variables

4.7.1. Dependent variables

The magnitude of adverse reaction of benzanthine penicillin in those who are taking it on a monthly basis for prophylaxis.

4.7.2 Independent variables

Age, sex, place of residence, duration of the disease since diagnosis, duration on benzathine penicillin before the reaction, , injection technique of BPG, sign and symptoms of adverse reaction, history of self or family history of allergy, previous history of drug allergy

4.8. Data Collection Instrument

The data were collected using a structured questionnaire, which was adapted from previously published studies with some modification to ensure applicability to our current study, validity and reliability. The questionnaire consisted of socio-demographic factors, clinical presenting symptoms of BPG adverse reaction and impact of adverse reaction.

4.9. Data Collection method

Principal investigator collected the data, patient phone address was identified from patient charts and the principal investigator did the phone interview .

4.10. Data Quality Assurance

The primary investigator examined the appropriateness of the methodologies followed. Data was collected exclusively by the principal investigator. The questionnaires were pretested on 5% of the sample in a different setting, the result of which was not included in the analysis. The study was done as per the ethical code of conduct.

4.11. Data Analysis Procedure

The data was entered using SPSS version 25 for analysis. Data cleaning and screening was conducted exclusively by the principal investigator. Any error in the data was cleaned. Descriptive summary measures were presented using Tables and Figures. Categorical data was analyzed using numbers, percent and ratio, while continuous variables was calculated with Mean and Standard deviation. The strength of statistical association was measured using binary logistic regression and 95% confidence intervals and statistical significance considered at $P < 0.05$

4.12. Operational Definitions

An adverse reaction is a response to a drug that is noxious and unintended and which occurs at doses normally used in for the prophylaxis, diagnosis, or therapy of disease or for the modifications of physiologic function. The onset of the adverse reaction may be sudden or develop over time(5).

The pharmacological classification includes two major subtypes,
Type A which are dose-dependent and predictable (non-immunological) and
Type B(immunological-allergic) reactions are unpredictable and not dose-dependent. The symptoms will be taken as an adverse reaction if they occur immediately following the reaction or within 24 hr of injection and if they were not there before the injection.

4.13. Ethical Clearance

The data collection was anonymous, which didn't include individual participant names and any other personal identifiers. Verbal consent was obtained from the participants before data collection. Ethical clearance was obtained from the Department Research and Publication Committee, at TASH, department of pediatrics and child health. Permission was also secured from the TASH outpatient department. As per our ethical review board, verbal consent was acceptable and thus approved per the protocol. Besides, confidentiality was ensured by omitting patient identifiers and giving code numbers.

4.15.Dissemination of results

The findings of the study will be shared with the staff of the department, it will be presented at the annual research conference of the college in local and international conferences and it will be forwarded for peer review and publication.

5. Results

5.1 Sociodemographic characteristics

In this study, 460 participants were interviewed, making a response rate of 100 percent. 47.4% of the participants were in the age group of 15-30 years, with the mean and SD of 23.8±9.5 years, respectively. Three hundred and twenty-eight (71.3%) of the participants were female, and 338(73.5%) were orthodox in religion, and 57.2% were from Addis Ababa.

Table 3. The sociodemographic characteristics of RHD patients on monthly benzathine penicillin Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, December 2020 - October 2021

Variable	Frequency	Percentage%
Age		
5-14	103	22.4
15-18	61	13.3
19-30	157	34.1
≥ 31	139	30.2
Sex		
Female	328	71.3
Male	132	28.7
Religion		
Muslim	77	16.7
Orthodox	338	73.5
Protestant	45	9.8
Residence		
Addis Ababa	263	57.2
Out of Addis Ababa	197	42.8

5.2 The study participants medical characteristics

Concerning the medical characteristics, in 83.3% of participants, the duration since RHD diagnosis ranges from 6month-10years. All of the participants took BPG, and out of them, 83.9% took it for a duration of 6month to 10years, and 100% of them took it through the IM route.

Table 2-medical characteristic of RHD patients on BPG Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, December 2020 - October 2021

Variable	Frequency	Percentage(%)
Duration since diagnosis of RHD		
≤ 6month	13	2.8
6month-10 years	383	83.3
11-20 years	56	12.2
≥ 20 years	8	1.7
Duration of benzathine penicillin before the ADR		
≤ 6month	12	2.6
6month-10 years	386	83.9
11-20 years	54	11.7
≥ 20 years	8	1.7

5.3 The prevalence of benzathine penicillin adverse reaction

In this study, out of 460 participants, 95(21%) of them developed adverse reactions.

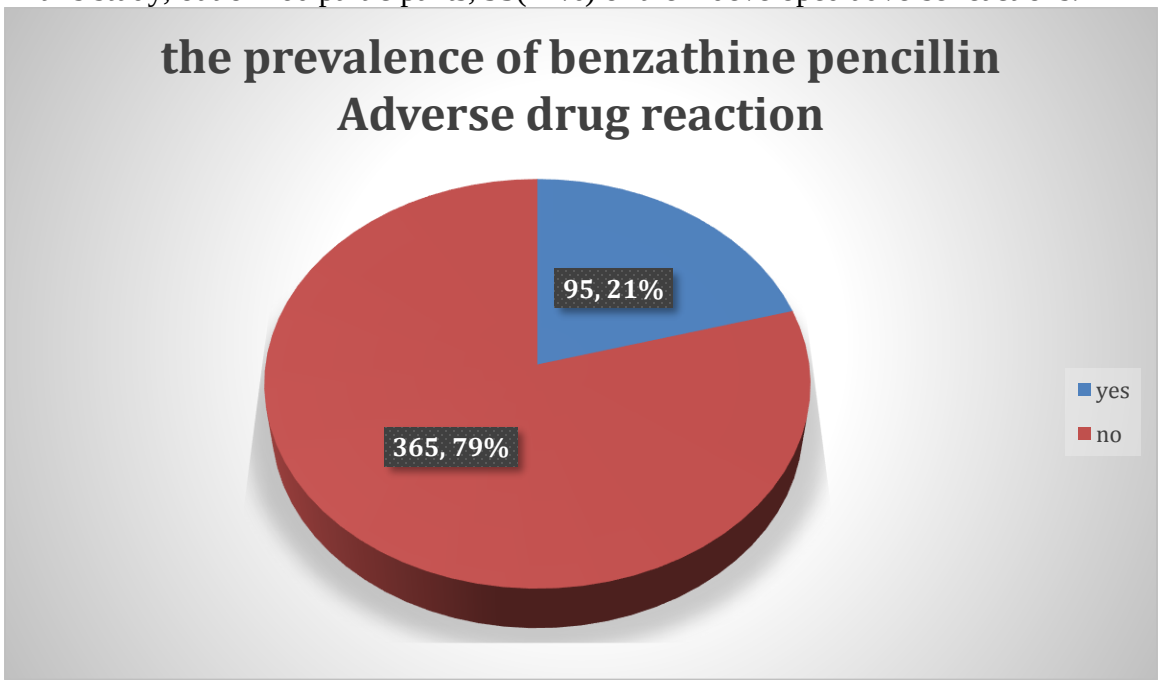


Figure 1. the prevalence of benzathine penicillin adverse drug reaction among RHD patients TikurAnbessa Specialized Hospital, Addis Ababa, Ethiopia.December 2020 -October 2021.

5.4 Characteristic of adverse drug reaction

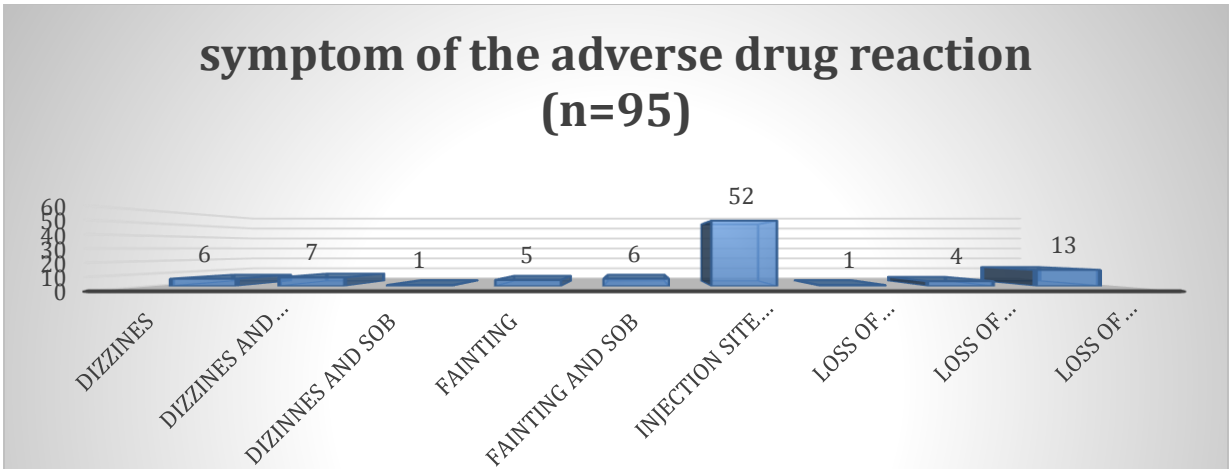
According to the study, 38.9% of the drug reaction cases occurred during injection, and in 56.8%, the reaction onset was within 24hours after taking the injection.

Table 3. Characteristics of adverse drug reaction of BPG in RHD patients TikurAnbessa Specialized Hospital, Addis Ababa, Ethiopia.December 2020-October 2021.

The time of onset of the adverse reaction after taking the injection	frequency	percentage
Within 24hr	54	56.8
Within one min	24	25.3
Within an hour	17	7.9
Receive any treatment for adverse effects (n=95)		
Yes	2	2.1
No	93	97.9
Was there a similar prior symptom before the ADR		
Yes No	0 95	0 100
Did you continue receiving injections after the ADR		
Yes	94	98.9
No	1	1.1
Have you had any similar symptoms if you are continuing the medication (94)		
Yes	51	54.2
No	43	45.8
Did you ever discontinue your injection any time for any other reason		
Yes	54	12.1
No	389	87.9
If yes, what was the reason (54%)		
Health Professional Refusal	19	35.1
Pregnancy	4	7.4
Unavailable	31	57.4
Did you observe or face any injection technique difficulty while receiving the injection		
Yes	6	2.3
No	454	98.7
If yes, what was the injection technique difficulty (n=6)		
Don’t give in lying position	1	16.7
Don’t mix well	1	16.7
Don’t use lidocaine	3	50
Inject many times	1	16.6
Is there any known medication you are allergic for		
Yes	-	-
no	460	460

5.5 The symptom characteristics of adverse reaction of BPG

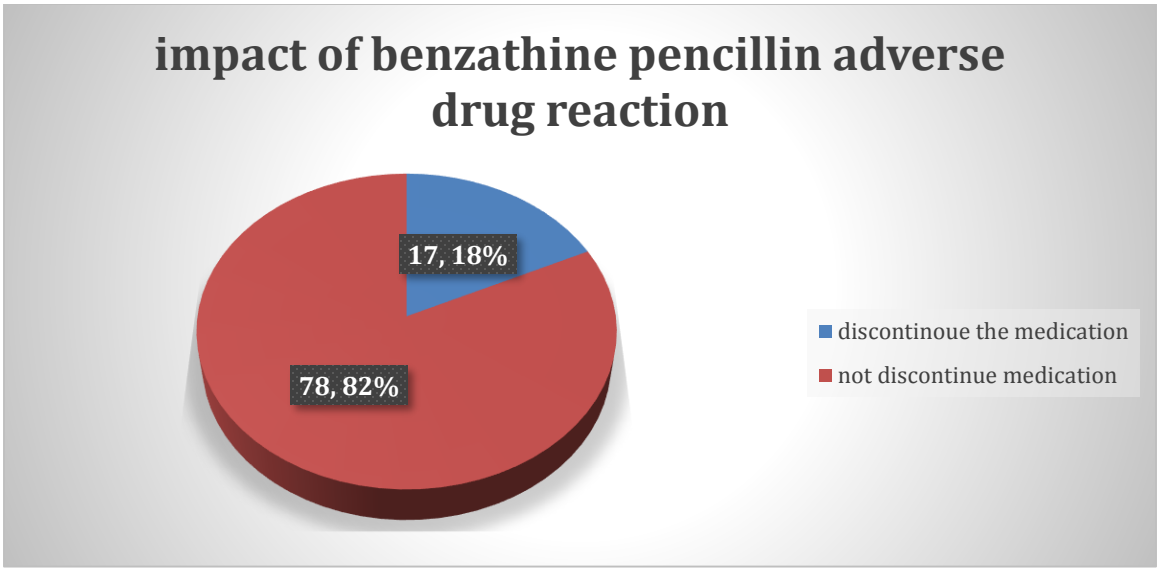
From those who develop ADR, 54.7%(52) develop injection site swelling, which is followed by loss of consciousness - 13.7%, fainting -6.1%, dizziness -6.1%, which is shown in the figure below



	dizzines	dizzines and fainting	dizinnes and SOB	Fainting	fainting and SOB	Injection site swelling	loss of conciousness, dizzines	loss of conciousness, leg swelling and SOB	loss of conciousness, dizzines
symptom of the adverse drug reaction (n=95)	6	7	1	5	6	52	1	4	13

5.6 The impact of benzathine penicillin adverse drug reaction

The impact of adverse reaction show that 17.8% of those who develop the ADR(21%) discontinued their medication for a range of 3 to 6 month. one participant totally discontinued the injection because of the ADR.



Of all participants, 12.1 % discontinued their injection for different reasons and amongst which a35.1% were due to health professional refusal and 57.4% were due to unavailability of the benzathine penicillin.

5.7 The determinate variable for the occurrence of ADR

The strength of association both dependent and independent variable assessed using odds ratio and 95% CI, accordingly, from participants, whose age range from 15-18 years had 3.2 fold increased risk to develop benzathine penicillin adverse drug reaction than from the age group of 5-14years (AOR=3.2, 95%CI=1.07, 18.62) and age range of 18-30 years had 9.2 fold times increased risk to develop adverse drug reaction compared to age range of 5-14 years(AOR=9.2, 95%CI=3.51, 19.49).

Table 4. The dependent and independent variable relation using logistic regression on benzathine penicillin adverse drug reaction TikurAnbessa Specialized Hospital, Addis Ababa, Ethiopia.December 2019 -October 2020.

Variable	BPADR		P-value	COR	P-value	AOR
	yes	No				
Age of the study participants						
5-14	4	99	1		1	
15-18	15	46	0.000	8.1(2.54, 25.67)	0.042	**3.2(1.07, 18.62)**
18-30	36	121	0.000	7.4(2.53, 21.39)	0.041	9.2(3.51, 19.49)
>30	40	99	0.000	10(3.45, 29.1)	0.094	12.8(0.94, 14.62)

sex of the patient						
female	80	248	1		1	
male	15	117	0.002	0.4(0.22, 0.72)	0.049	**0.56(0.29, 0.97)**
Residence						
AA	73	190	0.000	3.1(1.82, 5.14)	0.002	**2.4(1.38, 4.29)**
AUT OF AA	22	175	1			
Time to diagnosis of cardiac illness						
<=6month	0	13	**		**	
6month-10 years	75	308	0.049	0.24(0.06, 0.99)	0.393	0.28(0.01, 5.28)
11-20 years	16	40	0.232	0.40(0.09, 1.79)	0.298	0.43(0.09, 2.12)
>20 years	4	4	1			
Time of start BPG						
<=6month	1	11	0.057	0.09(0.01, 1.08)	**	
6month-10 years	75	311	0.048	0.24(0.06, 0.99)	0.843	1.3(0.10, 15.76)
11-20 years	15	39	0.214	0.39(0.08, 1.74)	0.056	0.29(0.15, 8.14)
>20 years	4	4	1	1		

6. Discussion

This study shows that adverse events following BPG injections occur in the setting of ARF prophylaxis. Previous reports were largely anecdotal,. This study has improved these descriptions and tried to see contributing factors for the adverse reaction.

In this study, the finding shows that 95 participants(20.6%) developed benzathine penicillin adverse drug reaction, This finding is not in line with 3.2% incidence reported by international Rheumatic fever study group(30) and also 1.4% incidence observed in nepal study.Also this finding is not in line with a study done in turkey in children with reported incidence of 0.18%(40). The possible explanation for this could be the adverse reaction in our study are patient symptom report.

The duration of cardiac disease in majority of the participants (83.3%) range from 6 month to 10 years ,and also the duration on benzathine penicilline before developing the ADR in 83.9% ranges from 6 month to 10 years ,this means the patients had been repeatedly exposed to BPG prior to the adverse event. This finding is also in line with the previous study done in Israel and Switzerland(37).

The onset of the adverse reaction symptoms range from within a minute to within 24hr after injection, And 51% of the participants who continued their injection after the adverse reaction had repeated symptom of adverse reaction.. This finding is similar with USA ,texas

47.3% are in the age range of 15-30.While looking into the study conducted in Israel study, age was not the associated factor for the adverse reaction(37), the possible explanation for this is our sample size is higher compared to the Israel study which involve only 9 cases.

Participants whose age range from 15-30 year has strong association with adverse reaction. This study is in line with nepal study(40).Also male participants were 44% less likely of developing benzathine penicillin adverse drug reaction than female participant.

Also, our study shows that the most common symptom of the adverse drug reaction is injection site swelling and pain which accounts for 54% of the ADR reported symptoms followed by loss of consciousness. There is no study to compare this result.

In our study there were no dermatologic reactions. So our finding is in line with the study done in Israel and Switzerland(37).

In our study its challenging to determine the magnitude of anaphylaxis because we need both sign and symptom to diagnose anaphylactic reaction based on the above aforementioned criteria. So we took the reported symptom as non-anaphylactic minor reaction. This is in line with a study done in Israel (30).

Regarding the impact of the adverse reaction on the follow-up,17% discontinued their monthly injection because of the adverse reaction and the time range that they discontinued ranged from 3 to 6month and reinitiated thereafter.there is no similar study done to compare this result.

Also, in this study, we assessed any injection-associated technique difficulty, and only 6 participants out of the total 460 reported that there was injection technique difficulty during mixing of the medication and during the IM injection. Three participants responded that the injection was given without lidocaine, but this was reported by the one who developed the reaction and the one who didn't. So this doesn't implicate its direct, contributory factor to develop the reaction. Also, in the study from Israel, they didn't find a direct correlation to develop the adverse reaction(37).

All patients described in our case series, including the children, had an underlying cardiac condition, which might have contributed to the serious adverse reaction. Similar to the study conducted in Australia, they showed that the underlying structural cardiac disease itself predisposes to adverse outcomes (38).

In our study we found that the overall adherence to the BPG, is 84.6%, and this is comparable with the study done in TASH on adherence to BPG in 2017, which shows the average adherence rate was 80.6%.(26).

7. Conclusion

In this study, Adverse drug reaction after benzathine penicillin is common . Factors which are associated with high rate of adverse reaction are age range of 15-30,female sex and self and family history of allergy.

8 Limitation and recommendation

8.1 Limitation

- Phone tracing is a challenge by itself because it has recall bias
- Also, there is no previous research on the topic in our setup to compare with
- Its challanging to confirm adverse reactions with only reported symptoms.
- There is no laboratory to confirm adverse drug reactions.

9.Recommendation

Based upon the significant outcomes obtained from the research outlined in the previous sections, the proceeding recommendations were made:

1.This study will be an entry point to give awareness to the health professional about the prevalence of BPG adverse reactions, and this will help to improve the overall care of the patient.

2. Efforts should be made to reduce the pain of BPG injections and should be given by trained professional

3.Adverse reactions should be reported to the pharmacovigilance programs where they exist.

4. This study will be a clue to make further qualitative study

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Annex Part I

Information sheet

Addis Ababa University College of Health Sciences Department of Pediatrics and Child Health

Title of the study: prevalence of benzanthine penicilline adverse drug reaction in RHD patients who are on monthly benzathine penicilline.TASH, Addis Ababa, Ethiopia.

Introduction

Hello!! Dear participants, this questionnaire was prepared by Hanna mekonnen, a 3rd Year pediatrics resident in Addis Ababa University, to assess the prevalence of benzanthine penicilline adverse drug reaction in RHD patients who are on monthly benzathine penicilline. Tikur Anbessa specialized hospital. During the study, you will be asked the following different questions.

Purpose of the study

The study is designed to assess the prevalence of benzanthine penicilline adverse drug reaction in RHD patients who are on monthly benzathine penicilline and to identify possible risk factors associated with it. This will provide baseline information to find out the prevalence and the possible associated factor of ADR and its impact.

What participation involves

During your participation in the present study, you will be interviewed certain questions on your personal information such as age, sex, religion, place of residence and also questions designed to assess prevalence and risk factors.

Confidentiality

The information you give through the phone intervie will be used solely for the purpose of the research and will not be shared with a third party under any circumstance.

SECTION A;

Socio-Demographic Part

1. gender A) male B female
2. Age
3. Religion
4. Place of residence
5. When was the time you were diagnosed to have RHD?
6. Do you take monthly benzathine penicillin?
7. When did you start taking monthly benzanthine penicillin for your heart disease?
8. With what route are you taking the injection IM or IV ?
9. Have you had any adverse drug reactions before?
10. If yes, when was the time you had the adverse drug reaction?
11. At what time was the onset of the ADR after the injection?
    a. Within a min
    b. Within 1 hr,
    c. Within 24 hr,
    d. >24hr
12. How long did the ADR last?
13. What was the symptom of an adverse reaction?

- Skin rash
- Flushing
- Dizziness or light-headedness
- Vomiting
- Diarrhea
- Fever
- Swelling and pain on the injection site
- Red and itchy eyes
- Persistent dry cough
- Hoarse voice
- Difficulty to breath
- Sensation of throat closure

- SOB
- Runny nose
- fainting
- loss of consciousness
- Itching
- Blistering, ulceration and sloughing of skin

14. Have you had these symptoms prior to taking the injection?

15. Did you receive any treatment for your adverse reaction?

16. Have you continued taking the drug after the adverse reaction?

17. If yes, what was the effect? Was there any similar symptom?

18. Have you ever discontinued ur injection because of the ADR?

19. If yes, for how long?

20. Have you ever discontinued ur injection because of any other reason other than ADR?

21. If yes, what was the reason and for how long?

22. Is there a history of self or family history of allergies?

የአማርኛመጠይቅቅጽ

ክፍል1. የታካሚየማህበረሰባዊባህርያቶችመረጃ

1) ጾታ ሀ) ወንድ ለ) ሴት

2) እድሜ

ክፍል2. የታካሚዎችአሉታዊምላሽባህርያትመረጃ

3) የልብበሽታእንዳለበዎትተመርምረውካወቁስንትአመትሆኖታል ?

4) የልብመድሃኒትመውሰድከጀመሩስንትጊዜሆኖታል ?

5) ስንትአይነትየልብመድሃኒቶችይወስዳሉ

6) በየወሩየሚወጋውንየቤዛንቲንፔኒሲሊንየልብመርፌይወስዳሉ ?

7) የልብመርፌውንየሚወስዱትበታፋነውወይስበደምስርነው ?

8) የልብመርፌውንእንደወሰዱአሉታዊምላሾችኖረውትያውቃል ?

9) አሉታዊምላሹከስንትሰዓትበኋላነበርየጀመሮዎት

ሀ/በአንድሰዓትውስጥ

ለ/ በ24 ሰዓትውስጥ

10) አሉታዊምላሹከስንትአመትበፊትነበርየነበረው ?

11) መድሃኒቱንከወደዱበኋላየትኛውየአሉታዊምላሽምልክትነበርየነበረዎት ?

የቆዳላይሽፍታትንፋሽማጠር

የቆዳመቅላትየአፍንጫፈሳሽ

ራስማዞርየድምጽመጎርነን

ማስቀመጥለመተንፈስመቸገር

ማስታወክየአይንመቅላትናማሳከክ

የቆዳማሳከክመርፌየተወጋበትቦታውሃመቋጠርናመላጥ

ትኩሳት

መርፌየተወጋበትቦታላይእብጠት

12) የልብመርፌውንከመወጋትዎበፊትቀደምብሎእነዚህምልክቶችነበረዎት**?**

13) የአሉታዊምላሽምልክቶችለምንያህልሰዓትቆየበዎት

14) የአሉታዊመላሹንምልክትእንዳዩህክምናአድርገዋልወይ? ውጤቱስምንነበር **?**

15) የአሉታዊምላሹንምልክትእንዳዩለጤናጣቢያሪፖርትአድርገዋል**?**

16) ከአሉታዊምላሹበኋላበየወሩየሚወስዱትንየልብመርፌአቁመዋል**?** ካቆሙስተጽኖምንነበር**?**

17) በየወሩየሚወስዱትንየልብመርፌእየቀጠሉከሆነምላሹምንይመስላል**?**

18) ከዚህበፊትለሌላየመድሃኒትአይነትአሉታዊምላሽኖሮዎትያውቃል**?** ካለስየምንመድሃኒትነበር?

19) ከዚህበፊትየምግብወይምየቆዳአለርጂኖሮዎትያውቃል?

20) በቤተሰብየመድሃኒትአለርጂያለበትሰውአለ? ካለስለምንአይነትመድሃኒት?