Cardiovascular Topic

Clinical and echocardiographic characteristics of patients who developed adverse events following Benzathine penicillin G injection for secondary prophylaxis of rheumatic heart disease: a cross-sectional study from three university hospitals in Ethiopia

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Abstract

Background: Intramuscular (IM) Benzathine penicillin G administration (BPG) is essential to prevent the progression of acute rheumatic fever (RF) to rheumatic heart disease (RHD). Fatal adverse events during BPG administration have been reported. This study aimed to characterise the clinical features and outcomes of RHD patients who developed adverse events with BPG administration for RHD prophylaxis in Ethiopia.

Methods: Charts of Patients who received BPG for secondary prophylaxis of RHD and had fatal adverse events were reviewed. An online survey was also used to collect data on adverse events during BPG injection. The study was done in Ethiopia at Ayder, Tikur Anbessa, and Jimma University Hospital from January 1, 2017, to May 30, 2023. Data were collected using a structured questionnaire. Demographic, clinical, and echocardiographic features were documented and analysed.

Results: All five chart review cases were female. Four of them had fatal adverse events. Four of them were aged > 18 years. All had clinical evidence of heart failure (HF) and echocardiographically advanced RHD, including severe tricuspid regurgitation (TR) and moderate to severe pulmonary hypertension (PHTN). Case 1 was 24 years old with severe mitral stenosis (MS). Case 2 was 19 years old with severe mitral regurgitation (MR). Case 3 was 14 years old with moderate to severe aortic regurgitation (AR) and moderate to severe MR. Case 4 was 43 years old with severe MS and moderate MR. Case 5 was 16 years old with moderate-severe MS, severe MR and atrial fibrillation. Four had received BPG before the event with no previous adverse reaction. None of our cases met the Level 1 Brighton criteria consistent with anaphylaxis. There were four deaths, three skin rashes, and one anaphylactic shock reported from the six RHD cases from the online survey.

Conclusion: We hypothesise that the coexistence of severe valve lesions with concomitant advanced HF may be an essential risk factor in BPG injection-related deaths rather than the presence of severe valve lesions alone. Heart failure and a failure of the compensatory mechanisms in BPG injection-related adverse circulatory reactions in advanced RHD with HF could be one of the major causes of these deaths. According to the literature, we recommend that patients with advanced RHD receive special attention regarding secondary BPG prophylaxis. For the introduction

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of less painful BPG injection, like the subcutaneous technique, further research is needed.

Keywords: BPG, RHD, adverse events, heart failure, Ethiopia

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Background

Rheumatic heart disease (RHD) is caused by rheumatic fever (RF), which develops after up to 3% of untreated Group A Streptococcal (GAS) infections. Though it is rarely acutely fatal, 40–80% of RF cases develop carditis, and 90% of these develop RHD.[1,2] The prevalence of RHD has been rising steadily, reaching 40 million people globally currently affected in 2021; this represents a 1.7-fold increase in prevalence since 1990.[3] RHD remains a significant public health problem in sub-Saharan Africa, including Ethiopia, and is one of the most common cardiovascular diseases in children and young people under 25 years of age globally.[1,2,4,6]

The cornerstone for preventing initial or subsequent attacks of RF and secondary prevention of RHD is the intramuscular (IM) injection of Benzathine penicillin G (BPG). It is generally reported that the procedure is so painful that the addition of a local anaesthetic is recommended during the injection.[5,4,7,9] BPG has been found to be approximately ten times more effective than oral antibiotic agents in preventing GAS pharyngitis and RHD progression.[8] Its use is associated with a lower incidence of recurrence of RF. Studies of RF cohorts suggest that prophylaxis allows for regression of valvular damage and may prevent death from RHD.[10-12] Penicillin is preferred to other antibiotics because it has a narrow spectrum of action, no known GAS resistance at present, and a lower chance of generating new antimicrobial resistance in the community compared to antibiotics with a broader spectrum.[5] Data from New Zealand shows that the serum concentrations of BPG in adults and children have not been, for most of the 21 days between the injections, at the level above 0.02 mg/L, which is considered necessary for secondary prevention of RHD.[13]

Penicillin drugs are among the most frequently reported causes of immune-mediated drug reactions. However, contemporary data about the prevalence of penicillin allergy are difficult to assess, given that penicillin allergy is widely over-reported. A review of allergic reactions after administration of BPG for RHD prophylaxis, in which most patients suffered from moderate to severe RHD and heart failure, showed an anaphylaxis rate of 0.27% and a mortality rate of 0.13%.[14,15]

Despite its crucial role, the existing market demand for BPG is projected to fulfil less than half of the actual worldwide requirement, and there is still a downward trend in manufacturing and supply.[3] This mainly affects the low-income countries with a high incidence of RHD.

Isolated reports of sudden deaths in patients with advanced RHD in close temporal relation to BPG IM injections have repeatedly raised the question whether contamination or poor drug quality could be the cause of these tragic events. Extensive research of the BPG preparations available on the international market has not revealed any serious quality defects that could be held responsible for such deaths, even though only one BPG product has been prequalified by the WHO and is on the WHO list of prequalified products.[3,16] Issues with administration techniques and the preparedness of health facilities and their professionals are also discussed.[7,17]

Marantelli *et al.* proposed four different hypotheses to explain fatal adverse events of BPG administration: Anaphylactic reaction, problems with BPG products, inadvertent intravascular administration of BPG, and the underlying structural cardiac disease itself predisposing to adverse outcomes. Pain or fear of BPG administration could drive a physiological response to initiate a vasovagal hypotension and syncope, a well-described reaction to intramuscular injection. In RHD patients with severe heart valve diseases, this reaction could lead to adverse events like circulatory arrest due to inadequate compensatory mechanisms.[18-20] As described by Wyber *et al.*, anecdotal reports of adverse reactions to BPG have been frequently reported at cardiology conferences for several years, underscoring physicians' concerns about potential quality issues and the role of vasovagal reactions to IM injections.[7] Detailed clinical and imaging features of such cases are lacking. A recent advisory from the American Heart Association has summarised the possible predisposing factors for deaths after BPG administration and has given recommendations on when to prefer oral Penicillin V over BPG.[21]

Colleagues from several hospitals in Ethiopia reported adverse events during BPG injection, leading to initial considerations of compiling these patient data from available sources in the country. The Ethiopian health professionals who had witnessed the death of adult and paediatric patients with RHD after BPG administration did not formally report these to the Ethiopian Food and Drug Administration, except for the two cases from the Ayder Comprehensive Specialised Hospital of Mekelle University in 2018, which were included in this study. There are only very few reports from different countries on the clinical characteristics of such patients and the circumstances of their death after IM BPG administration, and no reports have been collected in Ethiopia either. The present study addresses this topic and reports on the demographic, clinical, ECG, and echocardiographic characteristics of patients who experienced fatal adverse events after BPG injection for secondary prophylaxis of RHD. The study aims to describe possible clinical risk constellations for this type of death and other adverse events associated with IM BPG injections in RHD patients. For this purpose, medical records from three teaching hospitals in Ethiopia and seven Ethiopian hospitals that report their cases via an online survey are used.

Materials and methods

Study area and setting

This study was conducted in Ethiopia in the Ayder Comprehensive Specialised Hospital (ACSH) of the Mekelle University, College of Health Sciences, located in Mekelle, 783 km North of Addis Ababa, the Tikur Anbessa Comprehensive Specialised Hospital (TASH) of the Addis Ababa University, the College of Health Sciences and Jimma University Medical

Table 1. Study Method 1: echocardiographic and ECG findings of the four RHD cases who died following BPG administration

Parameters	*Case 1*	*Case 2*	*Case 3*	*Case 4*	*Case 5*
Echocardiography					
LA* diameter (mm)	47	51	38	NA[$,$]	NA[$,$]
LVEDD (mm)**	44	54	33	NA[$,$]	NA[$,$]
LVESD (mm)***	30	42	NA[$,$]	NA[$,$]	NA[$,$]
LV EF[#]	55%	61%	59%	NA[$,$]	NA[$,$]
Mitral stenosis (area in cm^2)	Severe (0.5)	No	Severe (1.5)	Severe	Moderate to Severe
Transmitral mean PG[##]	23mmHg				
Mitral regurgitation	No	Severe	No	Moderate	Severe
Aortic regurgitation	Mild	Mild	Moderate	No	No
Aortic stenosis	No	No	No	No	No
Tricuspid regurgitation	Severe	Severe	Severe	Moderate	Severe
PPAP[###] gradient (mmHG)	Severe (130)	Severe (70)	Severe (70)	Severe	Severe
Electrocardiography	P-Pulmonale & Mitrale; RAD[+], RVH[++]	P-Pulmonale, RVH	PVCs[$], ST-T changes	A.Fib[+++]	A.Fib[+++]

*LA: left atrium, **LVEDD: left ventricular end diastolic dimension, ***LVESD: left ventricular end systolic dimension, [#]LVEF: left ventricular ejection fraction, [##]PG: transmitral pressure gradient, [###]PPAP: peak pulmonary artery pressure, [+]RAD: right axis deviation, [++]RVH: right ventricular hypertrophy, [$,]PVCs: premature ventricular contractions, [+++]A.Fib: atrial fibrillation, [$,$]NA: not available

Center (JUMC) located in Jimma City, 352 km Southwest of Addis Ababa.

Study design and period

The study has two components. Data collection for both methods was conducted from 1 June 2023 to 30 June 2023.

Study method 1 is a mixed retrospective chart review of cases in the university hospitals who received secondary prophylaxis for RHD with IM BPG injections between 1 January 2017 and 30 May 2022, and who experienced fatal adverse events. The deaths of all patients except case 4 have been observed by either a resident physician or a consultant. Data were collected using a structured questionnaire from available sources of inpatients and outpatients, as well as ICU logbooks and hospital medical records. Age, gender, clinical characteristics, history of prior BPG injection, hospitalisations for heart failure, comorbidities, complications, dose, and type of BPG, time from administration of BPG to the onset of an adverse event, type of adverse event and outcome after BPG administration as death, possible cause, anaphylaxis, Level of Brighton Criteria, sign of a vasovagal syncope and the echocardiographic and ECG characteristics were retrieved from the patient charts when available. The Brighton Classification was used to assess whether anaphylaxis was present.[22]

Study method 2 was an online survey aiming to look for any deaths from BPG injection in the specified period in any patient in local Ethiopian Hospitals. The following data were collected: The name of the institution and the email address of the reporting health professional, the indication for the IM BPG injection, the time from the administration of BPG to the onset of the adverse event, the type of adverse event, and the emergency treatment given.

Results

Results from study method 1

There were four cases identified with fatal adverse events following BPG administration from the two tertiary teaching institutions in Ethiopia. Three cases were in ACSH, and two cases were in TASH. All were patients with RHD who received BPG as secondary prophylaxis. The fifth case from JUMC was not fatal and was wrongly declared to have a "Penicillin Allergy" as the reason for a collapse and resuscitation, as described later (see Table 1 & Table 2).

Case 1

A 24-year-old female was diagnosed with very severe rheumatic MS, mild AR, severe TR, and severe PHTN. Thyrotoxicosis was diagnosed on follow-up. She was put on furosemide 20 mg PO BID, spironolactone 25 mg PO daily, propylthiouracil 100 mg PO BID, and BPG 1.2 million IU IM monthly. She had repeated admissions at ACSH until the time of her death seven years later, the final three months before her death. Her chest X-ray, echocardiography, and ECG during one of her admissions revealed signs of advanced RHD (Figure 1 & Figure 2).

She had no history of adverse reactions to BPG. Three months after her seventh and last hospitalisation, she came for follow-up to the cardiac clinic of ACSH and was clinically stable. Powdered BPG was administered into the dorsogluteal muscle. Suddenly, following the injection, the patient complained of "heartache and chest pain" and arrested. Cardiopulmonary resuscitation (CPR) was performed, epinephrine, hydrocortisone, and atropine were administered, but she could not be salvaged. The patient died within a few minutes after the administration of BPG. She did not fulfil the Brighton criteria for anaphylaxis.[22]

Case 2

A 19-year-old female patient came for the first time to ACSH with severe rheumatic MR, severe TR, moderate PHTN and NYHA class IV heart failure and sinus rhythm in the ECG (Figure 3). She was put on furosemide 40 mg PO daily, metoprolol 12.5 mg PO daily, and BPG 1.2 million IU IM monthly. Since her initial diagnosis, she had repeated admissions for worsening HF. Six days after her last discharge from the emergency room, she came for follow-up to the ACSH cardiac clinic. BPG 1.2 million IU (6th dose) was given IM. Within one minute of the injection, she developed a loss of consciousness and urinary incontinence. She had cold extremities, her pulse was not palpable, and the pupils were dilated and non-reactive. CPR was done, adrenaline and atropine were given, and she was intubated, but it was not possible to resuscitate her. She did not meet any Brighton criterion for anaphylaxis.[22]

Table 2. Study Method 1: dose and type of IM BPG, administered time to onset of symptoms, prophylaxis after BPG administration, and outcome of patients with RHD who received BPG for secondary prophylaxis

Case	Age (years)	Dose of BPG	Type of BPG	Prior adverse events to BPG	Time from administration of BPG to onset of adverse event	Brighton criteria	Outcome
1	19	1.2 MIU	Powdered	No	Immediately	Didn't meet	Death
2	19	1.2 MIU	Powdered	No	1 minute	Didn't meet	Death
3	14	600,000 IU	Powdered	No	5 minutes	Level 2	Death
4	43	1.2 MIU	Powdered	No	Immediately	Didn't meet	Death
5	16	600,000 IU	Powdered	Powdered	Immediately	Didn't meet	Revived with resuscitation

IM: intramuscular, BPG: Benzathine penicillin G, RHD: rheumatic heart disease

Case 3

A 14-year-old female presented to ACSH with the diagnosis of RHD in NYHA class III HF with moderate to severe rheumatic MS, moderate AR, severe TR, severe PHTN, and a concomitant severe community-acquired pneumonia. She presented with shortness of breath, tachypnea, high-grade intermittent fever, and easy fatigability of three days' duration. The complaint of easy fatigability started five years back, and she had a history of leg swelling, which she didn't seek medical care for. Respiratory rate = 48 resp/min, pulse rate = 100 beats/minute, weight = 21.8 kg, height = 105 cm. She had coarse rales on both sides of her chest, a holosystolic murmur at the left lower sternal border, and the liver was palpable 7 cm below the right costal margin. Chest X-ray showed cardiomegaly with a cardiothoracic ratio of 70%, and echocardiography showed RHD with at least moderate AR, MS, severe TI, and severe PHTN, as shown in Table 1.

After two days of admission and treatment with IV antibiotics and diuresis, the patient was improving, and her respiratory rate = 24 resp/min, blood pressure = 100/60 mmHg, pulse rate = 90 beats/min, and oxygen saturation = 95% with room air. On the third day, the IV diuretics were changed to PO, vital signs remained stable, and the plan was to discharge her after giving BPG 600,000 IU IM. The patient had not previously received a BPG IM injection. She had no history of known allergies. Powdered BPG was administered IM while in the hospital. Within five minutes of the administration of BPG, she developed rapid breathing, tachycardia, hypotension with a change in mentation (pulse rate = 154 beats/min, respiratory rate = 60 resp/min, BP = 80/50mmHg, and she was desaturating to oxygen saturation = 80%. She was put on a face mask, oxygen, IV infusion of normal saline, adrenaline, and steroids were applied. Her condition deteriorated fast, and she was transferred immediately to the paediatric intensive care unit. There, she was intubated and mechanically ventilated. Despite the above measures, she died within five hours of BPG administration. Brighton Criteria: Level 2 (Probable case: One major cardiovascular criterion / Hypotension AND one major respiratory criterion / Tachypnea and Hypoxemia).[22]

Case 4

A 43-year-old woman was diagnosed in TASH with RHD 20 years ago. She was taking metoprolol, furosemide for HF and warfarin for atrial fibrillation. She regularly received BPG IM injections at a local health centre since RHD was diagnosed and

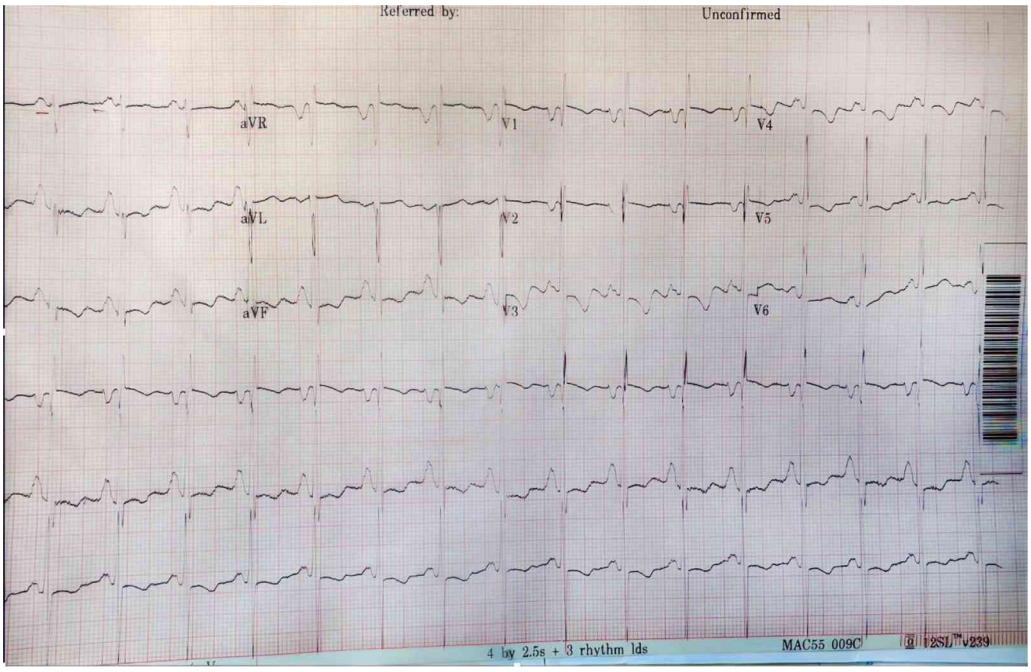

Figure 1. Electrocardiogram of Case 1

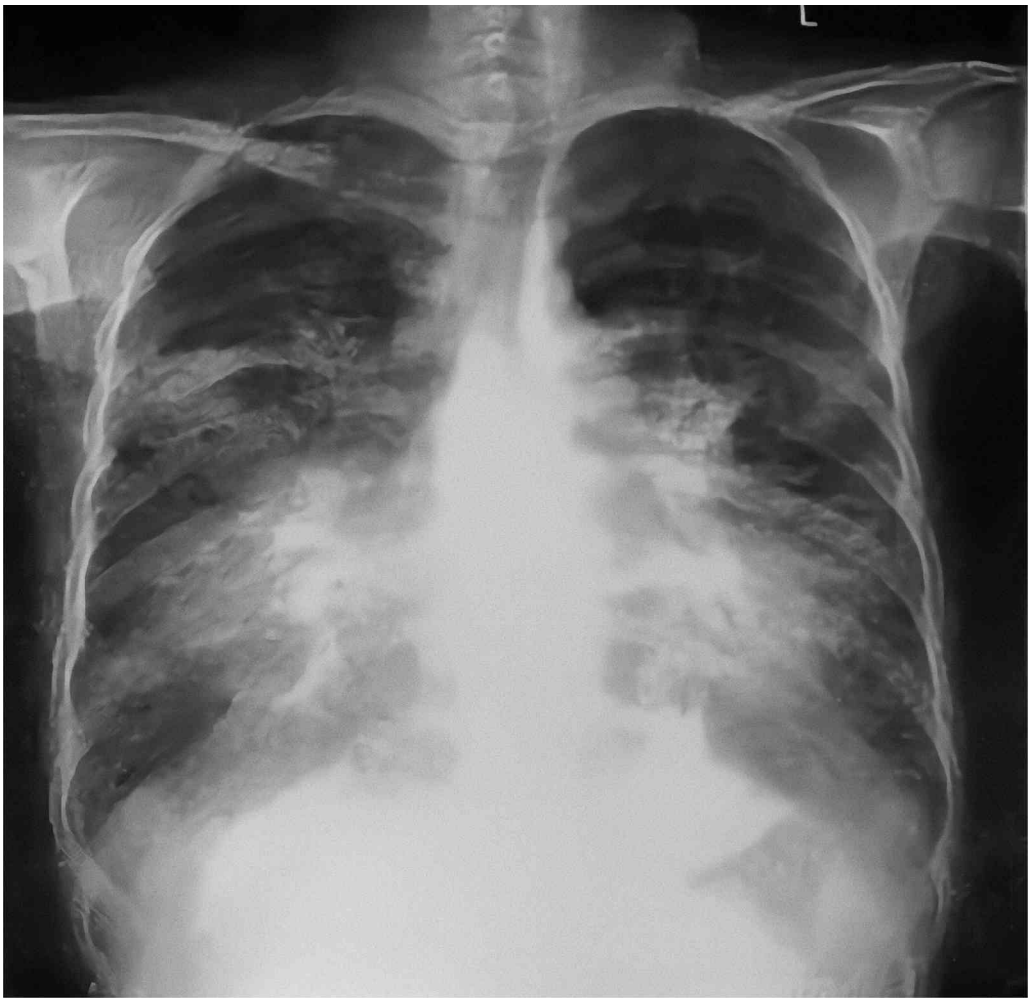

Figure 2. Chest X-ray of Case 1. The picture is reconstructed by Adobe Photoshop® Neural-Filter (2024) from a low-resolution hard copy printout. The original X-ray data had been lost in the electricity breakdown during the war in Tigray/Ethiopia 2021.

had never had an allergic reaction or fainted during previous injections. Echocardiography done a year before her death showed severe MS, moderate MR, and moderate TR with severe PHTN (Table 1). The ECG showed atrial fibrillation with a heart rate of 98 BPM. On her last injection of 1.2 million IU BPG IM, she suddenly collapsed immediately after receiving the BPG injection and could not be salvaged (history obtained from her sister). Her heart failure status was reported as stable, with no recent worsening. Most INR measurements were in the therapeutic range.

Case 5

A 16-year-old female was on regular follow-up in the Pediatric cardiac clinic of JUMC with the diagnosis of NYHA class III HF secondary to rheumatic valvular heart disease. There was moderate to severe MS, severe MR, TI, and PHTN. The ECG shows atrial fibrillation with right axis deviation and signs of right ventricular hypertrophy (Figure 4). She was on secondary BPG IM prophylaxis, on 40 mg furosemide three times a day and 600 mg KCL once a day.

When she came for her monthly BPG doses, she walked to the clinic and received 600.000 IU of BPG IM in the injection room by the nurses. Immediately after the injection, she collapsed in the injection room and required PCR, ventilation with a resuscitator, and IV fluid. She had no skin lesions. She responded to the procedure and resumed normal breathing and circulation. After observation for two hours, she was sent home walking. The team stated that she was "allergic to penicillin" and noted this in her medical record. She continued to take erythromycin PO for her secondary prophylaxis. Five months after this incident, she came to the same hospital emergency OPD with complaints of cough, fever, and shortness of breath. The emergency team diagnosed pneumonia in addition to heart disease and administered intravenous crystalline penicillin without considering the old hospital records that indicated "penicillin allergy." No adverse events were observed in her afterwards. The following day, her case was presented at the morning meeting, where it was determined that the original adverse event in the temporal context of the past BPG injection was not an allergic reaction to penicillin.

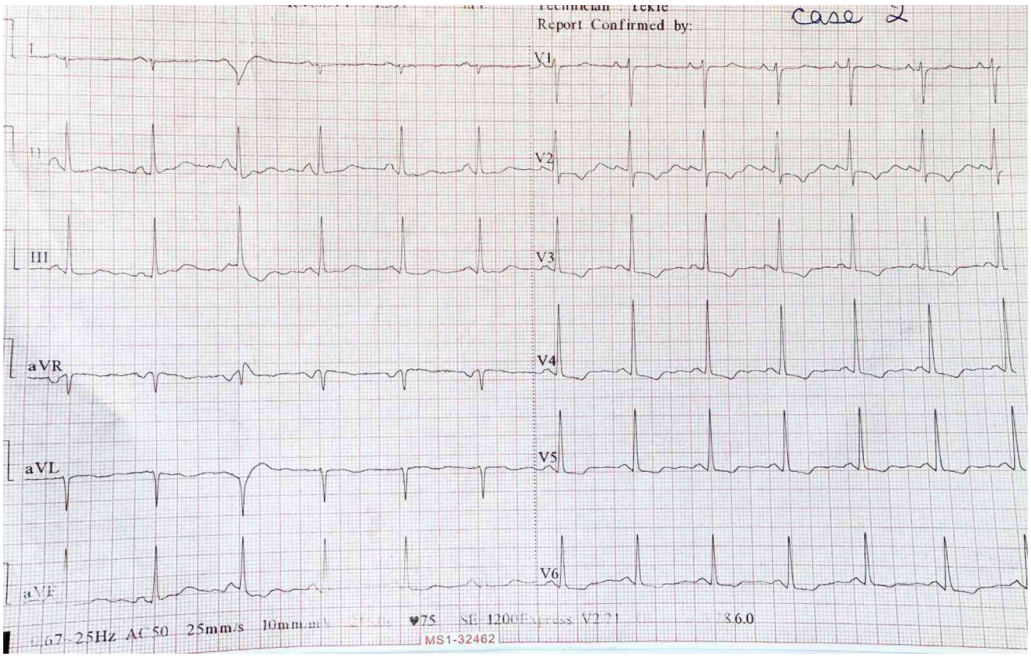

Figure 3. Electrocardiogram of Case 2

Of the five cases above, Cases 1 and 2 had been repeatedly hospitalised, while Case 3 was a newly diagnosed RHD patient who presented to the emergency room and was later admitted to the inpatient unit. Three of them had severe MS, and two with severe MR, one with concomitant moderate to severe MS. All had moderate to severe TR and severe PHTN (see Table 1 & Table 2). The administrations of BPG were made by trained nurses from the cardiac clinic, giving the same drug for more than eight years. They were trained with refresher courses as part of the national and regional training program of RHD control. Three of the cases collapsed suddenly and immediately after the administration of BPG. The resuscitation measures that were carried out were unsuccessful due to the suddenness of the incident and the severe heart disease. Case 5 was unique because the patient had been erroneously classified as allergic to BPG for years until she later tolerated crystalline penicillin without penicillin intolerance. In retrospect, this 16-year-old patient has survived a non-anaphylactic adverse event at an IM BPG injection.

Results from method 2

After an online data collection tool was developed, it was announced and shared at Ethiopian Medical Society meetings

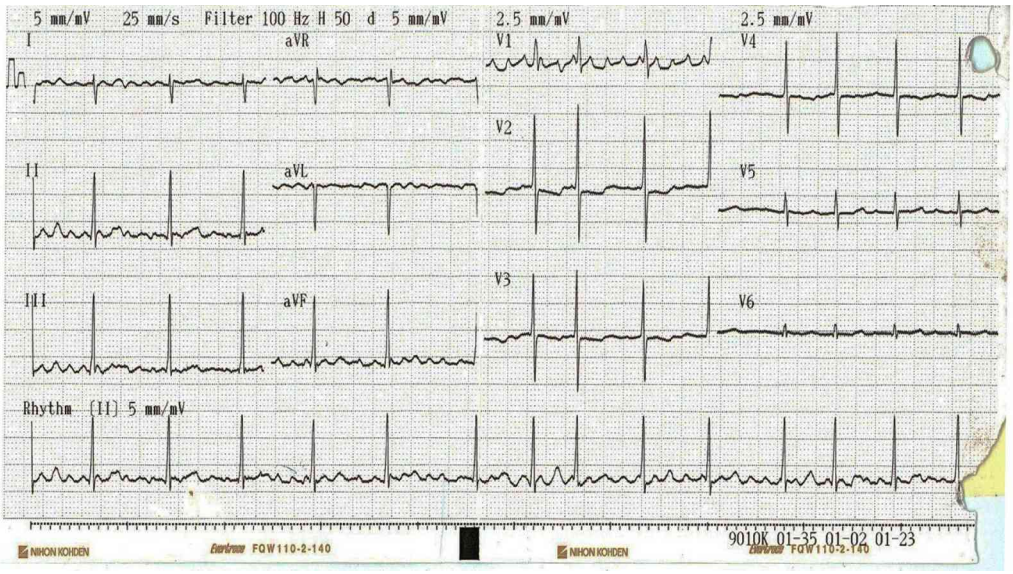

Figure 4. Electrocardiogram of Case 5

Table 3. Method 2: reported adverse events related to BPG administration

Case	*Name of health institution*	*Time from administration of BPG to onset of adverse event*	*Treatment given*	*Indication for the BPG injection*	*Side effect encountered*
1	Ameya Primary Hospital	5 minutes	Adrenaline	Tonsillopharyngitis	Skin rash
2	Aykel Hospital	Immediately	Adrenaline, IV fluids, intranasal oxygen	RHD/RF*	Death
3	Durame Hospital	Immediately	None	RHD/RF	Skin rash
4	Sude Primary Hospital	5 minutes	Adrenaline	RHD/RF	Anaphylactic shock
5	Bodit Primary Hospital	Not reported	Not reported	Tonsillopharyngitis	Skin rash
6	Chagni Primary Hospital	1 minute	Adrenaline	RHD/RF	Death
7	Chagni Primary Hospital	2 minutes	Adrenaline immediately, airway and CPR**	RHD/RF	Death
8	Health Centre, Addis Ababa	Immediate	Adrenaline and CPR	RHD/RF	Death#

*RHD/RF: rheumatic heart disease or rheumatic fever, **CPR: cardiopulmonary resuscitation, #data captured via in-person surveys in Addis Ababa health centres

and Ethiopian Cardiac Professional Society media platforms. In the study period, eight responses were received.

There were four deaths reported in this group with RHD or RF after receiving BPG IM for secondary prophylaxis. Only in Case 8, one of the RHD cases, detailed information was received: A 26-year-old male known for RHD had a follow-up at TASH for over 5 years. He was receiving BPG IM injections monthly at health centers and was on diuretics for HF with symptoms of congestion. On his last injection, he immediately collapsed. CPR was done, adrenaline was given, but the patient could not be salvaged. He had no skin lesions or abnormal body movements. A trained nurse provided the BPG injection. The patients who died had received the same batch of BPG that others had previously tolerated well.

In three patients, skin rashes and one anaphylactic shock after BPG IM injection were reported. Two cases of RHD and RF had a skin rash and an anaphylactic shock, which was managed, and the patients survived. Both patients with BPG for tonsillopharyngitis had only skin rashes (Table 3).

Discussion

In these two case series, we describe eight cases of fatal adverse reactions and one near-miss case associated with IM injection of BPG given as secondary prophylaxis to RHD or RF patients. In our study, five deaths were documented in patients with advanced RHD and heart failure. All of them required diuretics and some anticoagulants due to atrial fibrillation or repeated hospitalisations for concomitant diseases or recurrent chest infections. All four cases from Method 1 shared features of severe RHD plus symptoms of HF with clinical congestion, and three of them shared an additional history of recurrent hospitalisation. All of them had no allergic manifestations as defined by the Brighton criteria. Only Case 3 was classified as probable, meeting Brighton Criteria Level 2.[22] Although we did not have the complete clinical data for the patients in the group with Method 2, we see that only the group of RHD patients with BPG injection experienced events described as anaphylactic shock and death.

In agreement with Marantelli S. *et al.*, Sanyahumbi A. *et al.*, and Berkovic M.*et al.*, we consider severe valvular heart lesions as essential risk factors for adverse reactions to BPG injections.[19,21,24] Furthermore, we assume that concomitant diseases that further restrict cardiac performance, such as atrial fibrillation, manifest heart failure, repeated hospitalisations, and other unidentified concomitant diseases, are essential and complicating risk factors and not just the presence of severe rheumatic heart valve lesions. Until now, the availability, safety, and quality of BPG have been barriers to the prevention and control programs of RHD.[3] One of the often-assumed culprits for these immediate and unexpected deaths of patients who received BPG has been the quality of the drug itself, as was noted by both Marantelli *et al.* and Ali *et al.*[21,25] The first two cases from ACSH in this study were reported to the then Ethiopian Food, Medicine and Health Administration and Control Authority (EFMHACA) and the current Ethiopian Federal Drug Authority (EFDA) as soon as the adverse events occurred. A pharmacovigilance team investigated the reports, and a national committee was established to assess causality. After these first two reported fatal adverse events, the administration of BPG in Ethiopia was severely affected and temporarily stopped at the national level. The drug quality was tested abroad, with the preliminary conclusion at that time that the death of the patients could have been caused by anaphylaxis. The specific batch of the BPG was recalled from the Ethiopian market and replaced by a new manufacturer's brand. A letter was distributed to all Ethiopian regions stating the cautions that need to be followed when using BPG for RHD prevention, taking the necessary precautions during the administration of BPG, and reporting any event. It was also emphasised that trained professionals should administer the drug. This move was intended to encourage professionals to be cautious and vigilant when prescribing or administering BPG. However, dissemination of the information presented a challenge to the continued efforts to prevent RHD nationwide, and many professionals and patients remained hesitant to use BPG. Despite the change in the batch number of the drug, there was fear of resuming the administration of BPG by patients and professionals, and still, the effect is lingering. Historically, physicians' fear of anaphylaxis was found to be one of the major reasons for discontinuation of BPG prophylaxis.[26] Some states in India had banned BPG injections, given concerns about adverse reactions.[27]

The drug available in Ethiopia, which our patients received, was the low-cost lyophilised powder type of BPG. It has been reported that different brands of powdered BPG have distinct physical characteristics, including crystal shape and differences in solubility, which may affect the rates of needle blockage, among other quality issues. Clustered cases in Sudan lead physicians to consider that BPG quality may have contributed to the deaths.[19,25] Adverse events by proven BPG quality disruptions have not yet been reported.[16]

Accidental IV administration of BPG cannot be ruled out, but in all cases from the chart review, the injection was administered by experienced nurses in both adult and pediatric cardiology clinics and was reported as deep IM delivery. Intravascular passage of micro-crystals after IM administration is possible

and has been hypothesised to cause dyspnea, cyanosis, and neuropsychiatric symptoms (Hoigné Syndrome). However, this has been described mainly with procaine-penicillin, and the rapid onset and prominent cardiac conditions in our cases make this explanation unlikely.[24] Skin testing was proposed for patients receiving BPG for the first time.[28] In ACSH, skin testing has been introduced as a routine practice for patients since 2015, and due to its low practicability and availability, this was limited to a few cases. All cases in this study did not receive skin testing before the BPG administration. Ali *et al*. and Kado *et al*. stated that routine skin testing in a primary care setting is not recommended.[16,34]

In the 2022 American Heart Association Presidential Advisory statement, Sanyahumbi *et al.* reported sudden cardiac deaths in individuals with severe symptomatic RHD after BPG administration. They recommended that oral prophylaxis should be strongly considered in RHD patients at high risk of sudden death associated with BPG injection.[21] On the contrary, Wilson *et al.* from New Zealand responded that because of a total lack of cases of cardiac collapse in their very long-lasting and well-established cardiology program, they do not accept these recommendations of the AHA Advisory for their setting. They hypothesised that cardiac compromise could be due to severe decompensated RHD with co-existing advanced pulmonary hypertension, and a patient in New Zealand, contrary to most other endemic areas, would be subject to surgery. Therefore, they reiterated that they do not support adopting the AHA recommendations in New Zealand, as this could cause concern and lead to excess harm in the form of RF recurrence and loss of confidence in national secondary prevention programs.[30]

From our perspective, the AHA recommendation itself will be more than challenging to apply in areas like Ethiopia and other sub-Saharan African nations, where the recommended oral alternative, Penicillin V, is not available even for patients who present at a late stage of RHD, where a significant number of them belong to a high-risk group for receiving BPG.[19,21]

The authors of this article argue that the AHA advisory report may have categorised some RHD patients who tolerate BPG as high-risk. They have been following patients with RHD in Ethiopian teaching referral hospitals who were included in registries and clinical trials like the INVICTUS study.[31] The authors observed that individuals categorised as high-risk, such as those with severe rheumatic MS, even with PHTN but without hospitalization or significant clinical congestion, tolerated BPG well. In addition to excluding cases that could benefit from BPG, the AHA recommendation also leads to anxiety among healthcare professionals, patients, and their families and possible underuse of the most effective preventive RHD medication, BPG. This would be particularly unfortunate in settings where the underrecognised recurrence of RF is a major trigger of heart failure and, in turn, hospitalisation in countries such as Ethiopia and other sub-Saharan African countries.[33]

We are convinced that even subtle haemodynamic changes in the background of severe PHTN caused by the pain, anxiety, and subsequent vasovagal responses induced by BPG injection could be the reason for abrupt massive haemodynamic deterioration and deaths that would otherwise have been compensated for in patients without haemodynamic or clinical congestion, as Kotit *et al.* described.[20] These vagal reactions are likely exacerbated by conditions more common in low- and middle-income countries, where the majority of fatal BPG reactions have been reported.

To identify these RHD patients at increased risk, we propose further research into risk stratification based not only on the presence of severe valve lesions or symptoms alone. As stated by Sanyahumbi *et al.*, we reiterate that if BPG is preferred, it is to be given in settings with good resuscitation capacity and administered by well-trained health professionals. Therefore, it only remains the non-specific advice to pay particular attention to ensuring that the high-risk patients receive their BPG injections from particularly experienced health professionals, well-prepared and hydrated with as little stress and pain as possible, as described by Sanyahumbi *et al.* and the latest 2024 Sudan's rheumatic fever and rheumatic heart disease guidelines.[21,23,34]

In contrast to our cases, most of the above-cited publications did not include detailed descriptions of the duration of illness, symptoms, number of hospitalisations, ECG, and echocardiographic characteristics of the patients in whom the adverse events occurred. We believe further detailed clinical descriptions beyond those provided in this article are necessary to improve the timely identification and targeted pre-treatment of these high-risk patients for BPG treatment.

It is essential to develop better and longer-lasting formulations of inexpensive depot Penicillin than the BPG that has been in use for more than seventy years. In addition, less painful injection techniques of BPG with longer-lasting penicillin levels in the blood serum should be investigated and tested.[32] Initial studies by the Australian Telethon Kids Institute from 2018 to 2023 on the subcutaneous injection of BPG in prefilled glass syringes (Bicillin-LA®, Pfizer) have shown that this type of application technique was significantly less painful than the intramuscular technique in the study group and the preferred technique by the study participants.[35] In addition, the effective Penicillin serum concentrations of BPG in the participants were significantly higher and longer lasting, up to three months, in the setting of subcutaneous injection. These studies show such positive results that the applicability and success of the subcutaneous BPG injection should be investigated as soon as possible in the countries in Africa, Asia and other areas that are particularly affected by RHD.[13,29] We cannot advocate excluding the entire group of patients with the most severe degree of RHD from secondary BPG prevention without having made every effort to control the injection risk.

Strengths of our study

The deaths presented here have been witnessed and documented either by a resident physician or a senior consultant physician. Our study has done its best to address the issues of incomplete documentation. We used the logbook and chart review instead of clinician interview-based reports. This allowed us to report detailed clinical, ECG, radiological, and echocardiographic findings on the adverse events associated with BPG use in patients with RHD, which have been poorly described until now. This will help determine if a patient is at risk of anaphylaxis, as defined by the Brighton criteria, or an acute adverse event upon BPG IM injection. It also contains information about the preparations necessary to carry out resuscitation as successfully as possible in these rare, unpredictable, and abruptly developing haemodynamic emergencies.

Limitations of the study

This study shares the limitations of a retrospective chart review. Postmortem examination was not done for any of the patients. In the online survey, the severity of the valve lesions and the symptoms of HF were not communicated. It would have been desirable to include the complete medical data of all the cases and their specific situations directly before BPG injection, which were reported in the online survey, with sudden adverse events during BPG administration. In this way, it would have been possible to determine even more precisely which parameters characterise the patients who die suddenly from a BPG injection. The study was not designed to obtain information on the incidence and prevalence of this type of adverse reaction.

Conclusions and recommendations

The results of this review indicate that anaphylaxis was not the leading cause of death in these RHD patients in a direct temporal connection with an intramuscular BPG injection. There is no known evidence of contamination of BPG preparations as the cause of these negative occurrences. Following the current literature, we hypothesise that the acute adverse and lethal events described are most likely an acute and fatal impairment of cardiac function that may occur in association with painful intramuscular injection of BPG and cannot be compensated for in advanced RHD with manifest HF. All our cases showed signs of significant heart failure and additional clinical conditions that added to the ECG and echocardiographic parameters of advanced RHD-related changes. This makes it likely that this combination is the most important risk factor for death associated with BPG administration, rather than severe valve lesions alone. As a particularly feared reaction to the often-painful BPG injection, a vagal reaction is cited as a major trigger for the adverse current events. Further studies with more well-documented similar cases are needed to gain more certainty. Knowledge of such deaths has made healthcare professionals cautious and apprehensive about the use of BPG. Raising awareness among healthcare professionals and the community about the perception of high-risk patients is imperative. A proper setup for patient preparation, positioning, and resuscitation should exist where BPG injections are given to those who may develop severe adverse events. Reports on less painful subcutaneous injections of BPG, with longer-lasting, effective penicillin serum levels, could contribute to reducing adverse events following BPG injections.

Ethical considerations

Ethical approval was obtained from Mekelle University-College of Health Sciences, Addis Ababa University College of Health Sciences, and Jimma Medical Institute IRB review boards for each study site. Verbal informed consent was obtained from all the participants, including those in the online study. The study complied with ethical standards outlined in the Declaration of Helsinki.

Consent for publication

Not applicable

Availability of data and materials

Data is available from the corresponding author upon reasonable request.

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Authors' contributions

A.H.W., D.Y., and A.H. conceptualised the study and study design. D.Y. created the online survey tool and collated the online data, while A.H.W. and D.Y. drafted the questionnaire, which all authors approved. A.H.W., M.Y., S.B., A.L., T.D., A.H., and D.Y. collected the data from patient charts and reviewed online survey data. A.H.W., C.L., D.Y., A.H., and G.W. wrote the draft manuscript, which was later finalised by the contribution of all authors as they read and approved the final manuscript.

Conflict of interest statement

No potential conflict of interest was reported by the author(s).

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