LIDOCAINE AS A DILUENT FOR BENZATHINE PENICILLIN G FOR INJECTION PAIN IN CHILDREN WITH RHEUMATIC FEVER AND RHEUMATIC HEART DISEASE: A RANDOMIZED DOUBLE-BLIND CROSSOVER STUDY

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ABSTRACT

BACKGROUND: Rheumatic fever (RF) and Rheumatic heart disease (RHD) patients necessitate secondary prophylaxis with benzathine penicillin G (BPG) injection every 3 weeks to prevent recurrences and complications. Patients with rheumatic fever on regular benzathine penicillin G injection usually experience moderate to severe pain resulting to poor compliance to treatment.

OBJECTIVES: This study aims to compare the effect of BPG diluted in lidocaine hydrochloride 1% versus diluted water in reducing injection pain in patients with RF and RHD.

METHODS: This is a randomized double blind crossover study conducted at the PCMC OPD. Thirty-three patients diagnosed with RF and RHD were divided into 2 groups; the first group received BPG diluted in sterile water followed by BPG diluted in lidocaine hydrochloride 1% after 21 days, the second group received the same medications in reverse order. Pain scale was measured using Universal pain assessment tool immediately after injection. Paired T test was used to compare the pain score results of the two groups.

RESULTS: Pain score was significantly less in patients who received BPG diluted in lidocaine hydrochloride 1%; from an average pain score of 4.88 to 0.63 ($p<0.0001$), among those who received BPG diluted in sterile water. No adverse effects were seen in all patients.

CONCLUSION: This study concluded that BPG diluted in lidocaine hydrochloride 1% significantly and safely reduced post injection pain. In all patients diagnosed with RF and RHD, BPG injection should be diluted in lidocaine hydrochloride 1% to decrease injection pain and improve patient's compliance.

KEYWORDS: Rheumatic fever, Rheumatic heart disease, Penicillin, Lidocaine, pain

INTRODUCTION

Rheumatic fever (RF) and Rheumatic heart disease (RHD) are the most serious complications of Group A Beta Hemolytic Streptococcus (GABHS) infection. The prevention of both initial and recurrent episodes of acute rheumatic fever depends on controlling GABHS infections of the upper respiratory tract. Therefore, these patients should receive continuous antibiotic prophylaxis to prevent recurrences. 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.[1] Based on review of Zühlke, there is an overall global burden of 471,000 cases of RF annually, with a peak incidence of RF in children ages 5 to 15 years, ranging from 10 cases per 100,000 in industrialized countries to 374 cases per 100,000 in the Pacific region.[2] In the Philippines, incidence of rheumatic fever and rheumatic heart disease based on the Philippine Pediatric Society registry is 2553 cases since 2006.[3] Antibiotic prophylaxis for secondary prevention of rheumatic fever and rheumatic heart disease use benzathine penicillin G (BPG) 600,000 IU for children weighing less than 60 pounds and 1.2 million IU for those weighing more than 60 pounds.[1] In 2001 WHO Technical report on RF and RHD stated that intramuscular (IM) injection of benzathine penicillin every 3 weeks is the most effective strategy for prevention of recurrent attacks of RF.[4]

Compliance to treatment in secondary prevention of rheumatic fever is an important aspect in preventing recurrences. In the pediatric age group, pain associated with intramuscular injection of benzathine penicillin G is one of the factors affecting compliance. Many centers have tried different techniques to reduce injection pain with benzathine penicillin G. This study was conducted to answer the question: How effective Is lidocaine hydrochloride 1% as diluent for benzathine penicillin G injection in reducing injection pain in patients 10-18 years old with rheumatic fever and rheumatic heart disease as compared with sterile water?

Antibiotic prophylaxis for secondary prevention of rheumatic fever and rheumatic heart disease uses intramuscular benzathine penicillin G every 3 weeks and compliance to treatment is an important part of successful management. In patients receiving prophylactic benzathine penicillin G injection, one of the reasons that affected poor compliance was injection pain and decreasing injection pain may improve compliance of patients to regular injection and prevent further progression and complication of the disease. This study can help increase the awareness of pediatricians and provide options of using lidocaine hydrochloride 1% as an alternative to sterile water as diluent of BPG. This study can guide health policy makers in the Philippines in making future recommendations and clinical practice guidelines on RF and RHD treatment.

In patients diagnosed with RF and RHD, secondary prophylaxis is important to prevent recurrences and further complications. Secondary prophylaxis in these patients is given every 3 weeks for a minimum of 5 years. Thus, compliance to treatment for this long period of time is a challenge to our patients. There are many factors affecting compliance such as lack of funds for medication, lack of knowledge on the importance of prophylaxis and pain associated with injection every 3 weeks. Patients with rheumatic fever on regular benzathine penicillin G injection usually has pain scale of 8-10.[5] Some centers employ techniques to reduce the pain in IM injections, such as use of smaller gauge needles, direct pressure, slow injections and distractions. [6]

There were only two published studies which used lidocaine as diluent for BPG; a study done in 1998 and a study in 2012. Morsy et al did a a randomized, double blind crossover study among 100 patients with rheumatic fever in Egypt in 2012. BPG was diluted in lidocaine or sterile water and patients received both preparation, 21 days apart. Pain score was measured immediately after injection using revised faces pain scale. There was significant decrease in pain level immediately after injection; pain decreased from an average of 6.7 (range of 4 to10) in patients who received BPG

in sterile water to 5.2 (range 4 to 8) among those in which lidocaine was used as diluent. Serum penicillin levels were also measured in this study and there was no significant change in serum penicillin levels in patients given BPG diluted in sterile water compared to those who received lidocaine as diluent.[5] They concluded that lidocaine as diluent does not affect the efficacy of BPG and at the same time will effectively reduce injection pain.

In 1998, Amir et al did a randomized double blind crossover trial among 18 patients with rheumatic fever. In this study, BPG was diluted in lidocaine and sterile water. Pain was measured immediately after every injection. This study also showed significant reduction in injection pain, without altering the serum and urine penicillin levels.

The two studies included adolescent patients aged 10-19 years old to have more accurate assessment of pain with less variability. The two studies did not report any adverse effect or toxic effect to lidocaine when used as diluent.

Lidocaine is one of the most commonly used local anaesthetics. Lidocaine blocks activated and inactivated sodium channels with rapid kinetics. It stabilizes the neuronal membrane by inhibiting the ionic fluxes required for the initiation and conduction of impulses thereby effecting local anesthetic action.[7] It is a clear colorless, sterile non-pyrogenic aqueous solution. Its most common adverse effect, like those of other local anesthetics include locally at site of infection: mild bruising, redness, itching, or swelling where the medication was injected. Unlikely but serious side effects of Lidocaine, when given intravenously include drowsiness, mental/mood changes, ringing in the ears, dizziness, vision changes, tremors, numbness, headache, or backache.[8]

Lidocaine has been studied and used as a diluent in other medications given intramuscularly to reduce pain. Schichor et al (1994), did a randomized prospective study among adolescents who were culture positive for Gonorrhea, They were given IM Ceftriaxone diluted in either lidocaine hydrochloride or sterile water. Pain score was measured using a visual analog scale. This study showed that lidocaine reduced the injection pain of intramuscular ceftriaxone when compared with sterile water as a diluent.[9]

When using lidocaine as a local anesthetic, the maximum allowable dose is 4.5 mg/kg/dose up to 300mg. [10] In both studies by Morsy et al and Amir et al, lidocaine as a diluent for benzathine penicillin G was given at 3.2 mL, equivalent to 32 mg for every kg of the patient.

In the out patient department of a tertiary government hospital in Quezon City, there were an average of 70 patients diagnosed with rheumatic fever and/or rheumatic heart disease who have BPG injection every month. There were only 37 patients who have regular BPG injection every 21 days in 2015.

A study by Respicio et al in 2015 on the clinical profile and factors related to compliance with Benzathine Penicillin G Prophylaxis among RF/RHD patients at the Tarlac Provincial Hospital, Philippines. It was identified that the compliance rate of patients to treatment is at 46.6%. [11]

At the Philippine Children's Medical Center (PCMC) Out Patient Department (OPD), the current practice is diluting BPG in 4 ml of sterile water, which is the recommended volume of dilution of BPG based on the drug insert. If 4 ml of lidocaine will be used as diluent for BPG, it will be equivalent to 40mg for each patient, still within the maximum allowable dose.

Using lidocaine as diluent in IM medications is not yet a common practice in the Philippines. There are only 2 published studies that used lidocaine as a diluent for benzathine penicillin G, and no study was done yet in Southeast Asia including the Philippines.

In this study we aimed to evaluate the effectiveness of lidocaine hydrochloride 1% as compared to sterile water as diluent for benzathine penicillin G in reducing injection pain in patients 10-18 years old with rheumatic fever and rheumatic heart disease.

METHODOLOGY

This is a randomized double-blind crossover study conducted in Philippine Children's Medical Center Out Patient Department, a tertiary pediatric hospital in Quezon Avenue, Quezon City. Patients enrolled in the study were from the section of Pediatric Cardiology Out patient Department. The patients included in the study were diagnosed with rheumatic fever and rheumatic heart disease, 10 to 18 years of age, receiving benzathine penicillin G injection every 21 days, and with good compliance to injection for the last 6 months. Excluded in the study are RHD patients with severe valvar regurgitation/stenosis, with known sensitivity to lidocaine, and those non-compliant to penicillin injection. The sample size was computed based on the study by Morsy, et al, with the mean pain score for sterile water as diluent of 6.7, versus the mean score of 5.2 using lidocaine. Standard deviations were estimated using the following formula: $S = \frac{1}{12}\left(\frac{(a-2m+b)^2}{4} + (b-a)^2\right)$. STATA 11 was used to compute the sample size. To get a true difference at 0.05 level of significance and 80% power, a minimum sample size of 32 is needed, 16 participants in each group.

Patients were recruited in the study as they come for their BPG injection in the OPD. The primary investigator obtained informed consent (Appendix 1) from all parents or guardians and assent forms (Appendix 2) from patients. The patients were randomly allocated into 2 groups using a computer generated randomization list with Microsoft Excel which assigned patients to either group A or B (Appendix 3).

The duration of the study is for 3 weeks per patient; a total of 9 weeks for the whole study period. Patients were asked to participate in this study during their scheduled injection every 21 days for 2 consecutive follow-ups. Patients in group A received BPG diluted in sterile water in the first visit and diluted in 4 ml of 1% lidocaine hydrochloride in the second visit, 21 days apart. Group B received BPG diluted in 4 ml of 1% lidocaine hydrochloride in the first visit and BPG diluted in sterile water in the second visit. The BPG doses used was 600,000 IU for children weighing less than 60 pounds and 1.2 million IU for those weighing more than 60 pounds.[1]

The pharmacist prepared 2 sets of diluents for the nurse. Lidocaine hydrochloride 2%(Eurocaine by Euromed) was diluted in equal amount of sterile water to make lidocaine hydrochloride 1%. The diluent are both

colorless, clear solutions placed in identical vials. The sterile water and lidocaine hydrochloride 1% were labeled with either red or blue label by the pharmacist.

The nurse was blinded in giving either BPG diluted lidocaine hydrochloride 1% or BPG diluted in sterile water. The nurse in charge washed hands and prepared the materials. The upper outer quadrant of gluteus muscle, which is the injection site was uncovered and disinfected with alcohol circularly from inward to outward then air-dried. A gauge 21 needle was inserted swiftly at an angle of 90 degrees, and then aspirated briefly, if blood appears, needle was withdrawn and another site was selected. If no blood was aspirated, benzathine penicillin G diluted in either lidocaine or sterile water was injected slowly intramuscularly. The needle was withdrawn and a dry sterile cotton was placed in the post-injection site and secured with adhesive tape.[14] A single brand of penicillin (Zalpen by Cathay) was used in the entire study period and one nurse administered the medication to the patients.

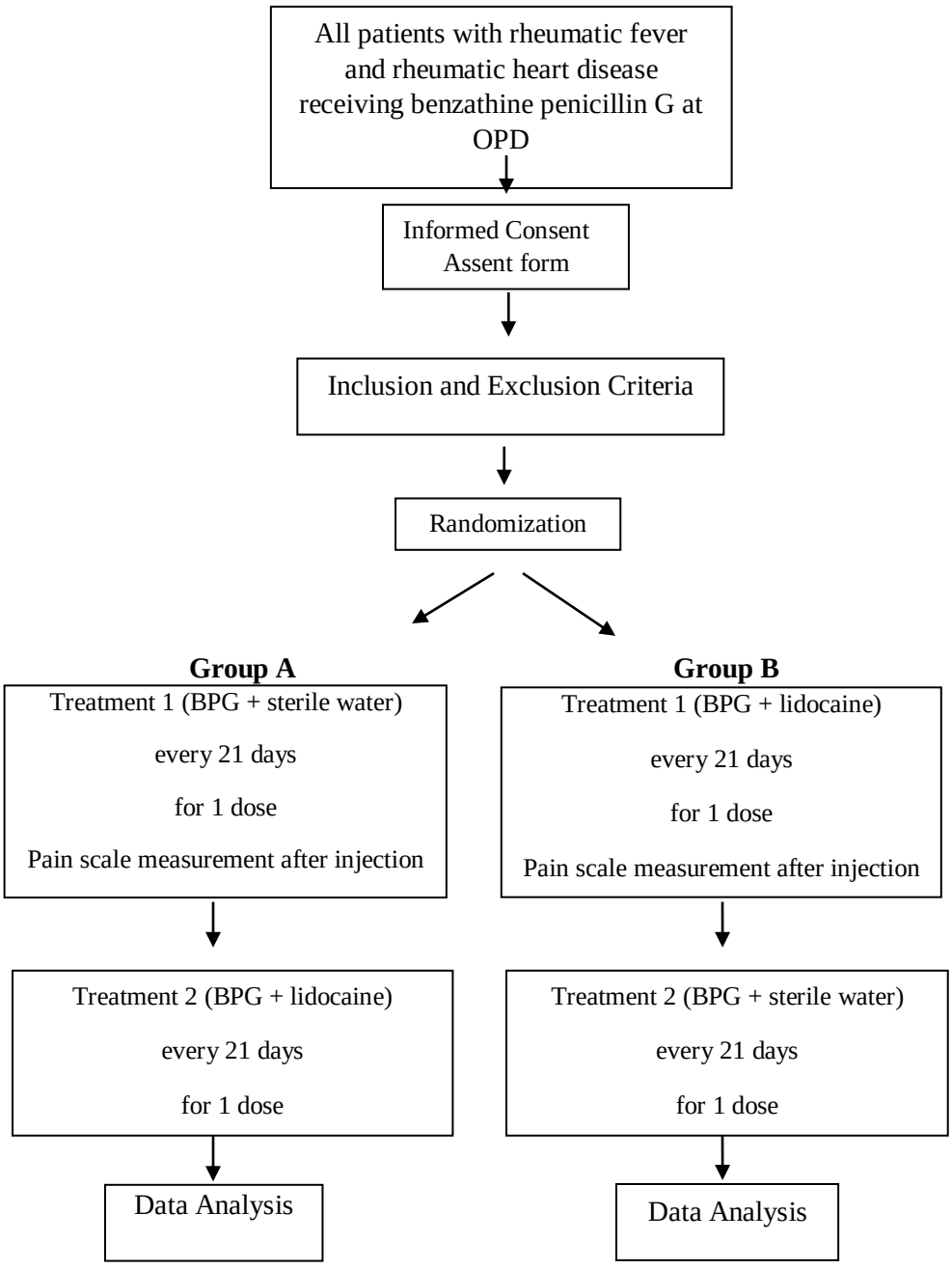
The physician, the patient and the nurse giving the medication were blinded on the patient randomization to either lidocaine or sterile water diluents. The pharmacist who prepared the medication is the only research member aware of the randomization.

Pain was measured using the universal pain assessment tool. Pain assessment was recorded immediately after injection by the primary investigator or the nurse-in-charge by asking the patient to identify the pain scale. The universal pain assessment tool (Appendix IV), was used in this study. It has a scale of 0 to 10 together with facial grimace scale, showing 6 faces from no pain to severe pain. The face and number scale was shown to the patient, but the number equivalent was recorded for data analysis. Pain scores were interpreted as follows: pain score 0: no pain, 1-2 pain score: mild pain, 3-6 pain score: moderate pain, 7-9 pain score: severe pain and pain score of 10 as most severe pain. Patients were observed at the out patient department within 1 hour from the time of injection for any adverse reactions such as generalized pruritus, wheals, flushing or any signs of anaphylaxis.

The baseline characteristics that were recorded in patient data form included the patient age, sex, diagnosis of rheumatic fever or rheumatic heart disease and duration of BPG treatment. In patients diagnosed with rheumatic heart disease, the specific valvular lesion was also documented.

Shown in Figure 1 is the outline of the study procedure.

Figure 1: Flowchart of Study Procedure



Descriptive statistics was used to summarize the clinical characteristics of the patients. Frequency and proportion was used for nominal variables and mean and SD for interval/ratio variables. Statistical analysis was computed using Microsoft excel. Paired t test was used to compare the results between the two groups and P value was set at ≤ 0.05.

This research was submitted, reviewed and approved by the IRB-EC prior to its implementation. Participants were recruited at the outpatient department of a tertiary

government hospital by the primary investigator. The subjects were oriented as to the purpose, nature and objective of the study. A written informed consent from parents and guardians and assent forms from patients are necessary prior to inclusion in the study.

All data gathered in this study was kept confidential. The primary investigator is not affiliated with any pharmaceutical company and did not receive any compensation for medications used in this study.

RESULTS

Sixty-five patients came for BPG injection during the study period. Forty-two patients were eligible for the study. There were 9 patients who did not consent to participate in the study. The 33 patients who participated in the study were randomized to group A, 17 patients and group B, 16 patients. All patients were able to follow-up on their scheduled date. There were more females than males in the study (2:1), with a mean age of 14.2 years old, range of 10-18 years old. Five patients were diagnosed with rheumatic fever and 28 patients diagnosed with RHD. Mild mitral regurgitation was the most common valvular involvement, comprising 17.9% of all RHD patients. All patients had regular BPG injection every 3 weeks before enrollment. These patients had an average of 43.6 months of BPG injection prior to enrollment in this study. Table 1 outlines the demographic characteristics of patient enrolled In the study.

Table I: Demographic Data of Rheumatic Fever and Rheumatic Heart Disease Patients (n=33)

	Mean ± SD
Age	14.27 ± 5.66
Sex	**Frequency (%)**
Male	11 (33.3)
Female	22 (66.7)
Diagnosis	**Frequency (%)**
Rheumatic fever	5 (12.2)
Rheumatic heart disease	28 (84.8)
Valvular Lesion:	**Frequency (%)**
RHD MR mild, AR mild, TR mild	1 (3.6)
RHD MR mild TR mild	4 (14.3)
RHD AR mild TR moderate	1 (3.6)
RHD AR moderate MR mild TR mild PR mild	1 (3.6)
RHD MR moderate, AI moderate	3 (10.7)
RHD MR mild	5 (17.9)
RHD MR mild AR mild	1 (3.6)
RHD MR mild TR mild PR trivial	1 (3.6)
RHD MR moderate	2 (7.1)
RHD MR moderate AI mild	1 (3.6)
RHD MR moderate AI moderate	3 (10.7)
RHD MR moderate AR moderate PR moderate	1 (3.6)
RHD MR moderate, AR moderate TR mild	1 (3.6)
RHD MR moderate, TR mild	1 (3.6)
RHD MS moderate MR moderate AR moderate TR mild PR mild	1 (3.6)
RHD TR moderate, MR moderate	1 (3.6)
	Mean ± SD
Duration of BPG treatment (months)	43.6 ± 11.31

As shown in figure 2, group A patients received BPG diluted in sterile water in first injection with an average pain score of 5.5, which means moderate pain. The pain score range from 0 to 10 ± 2.67. In comparison, in the second injection, BPG was diluted in lidocaine and the average pain score was 0.47, which means no pain. The pain score range from 0 to 2 ± 0.47. Comparing group A to group B patients, group B patients received BPG diluted in lidocaine first, with an average pain score of 0.81, no pain. The pain score range from 0 to 4 ± 1.16. In their second injection with BPG diluted in sterile water, the average pain score was higher at 4.12, moderate pain, with pain score range from 2 to 6 ± 1.36. Overall, the pain score was significantly decreased in all patients who received BPG diluted in lidocaine hydrochloride 1%; with an average pain score of 0.63, no pain, range from 0 to 4; ± 1.03 versus 4.88, moderate pain, range from 0 to 10; ± 2.23 in patients whose BPG was diluted in sterile water. The difference between the pain scores of patients who received BPG diluted in sterile water and who received BPG diluted in lidocaine hydrochloride 1% were compared, with mean difference of 4.24 (± 2.12), p value <0.0001, which is statistically significant.

Figure 2: Pain Score of Group A and Group B After Injection of BPG Diluted in Lidocaine and Sterile Water

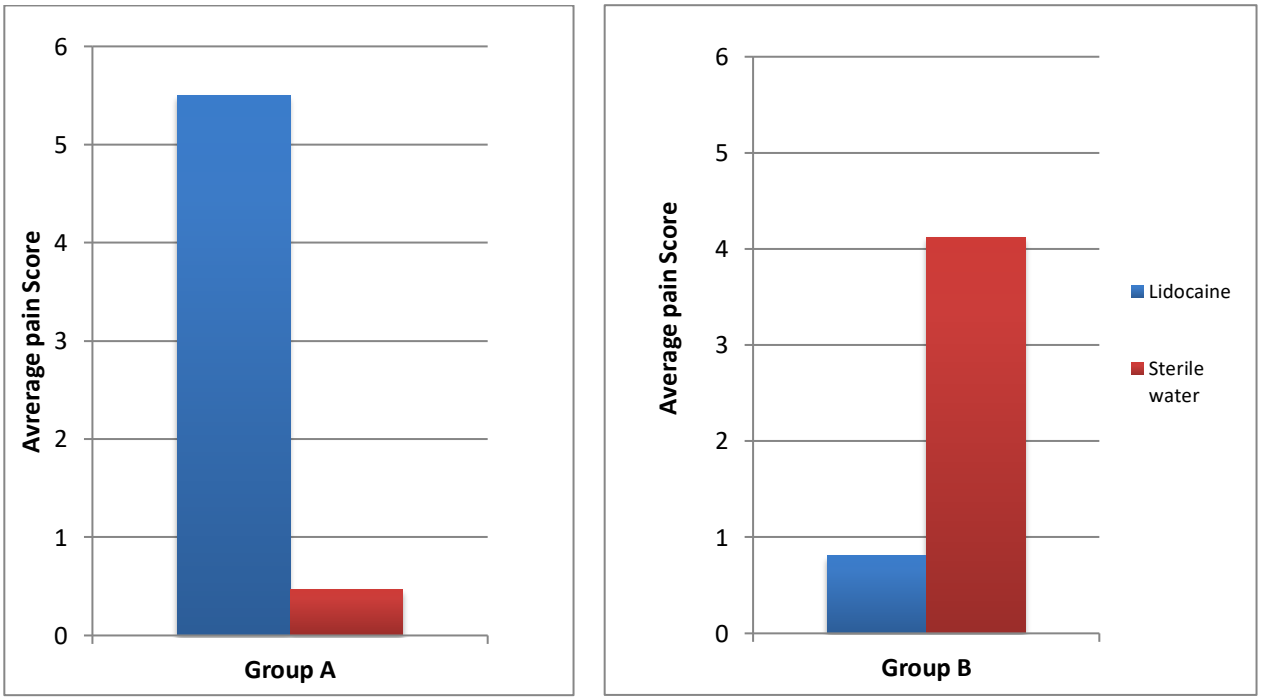
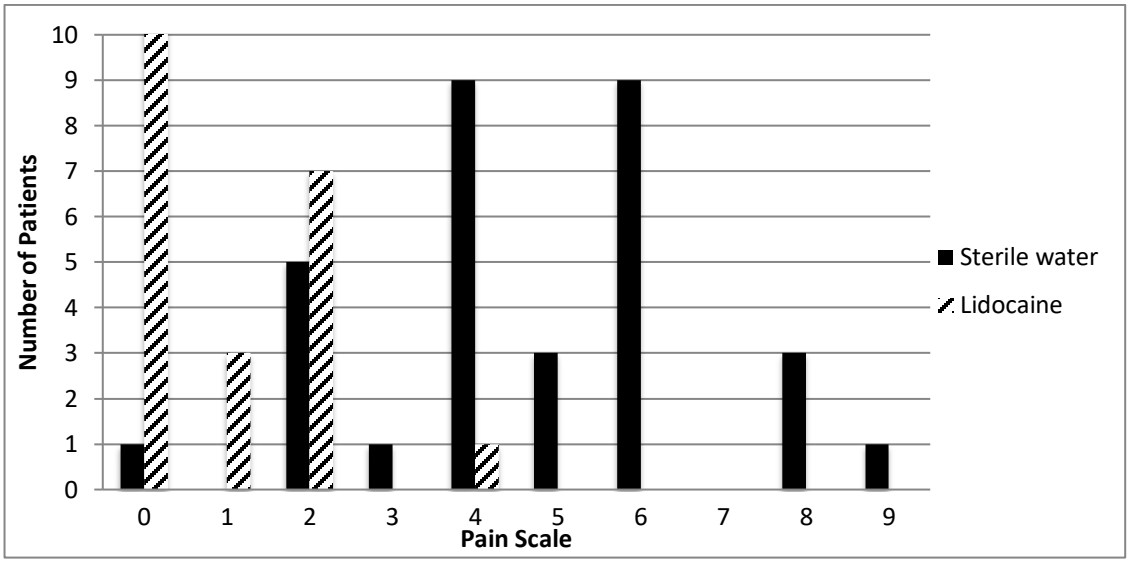


Figure 3 shows that after injection, 97% of patients who received BPG diluted in lidocaine hydrochloride 1% had pain score mainly in the value of 0 to 2. On the other hand, 55% of patients who received BPG diluted in sterile water experienced pain with score of 4 to 6. There was no adverse reaction noted in all patients who participated in this study.

Figure 3: Stratification of Patients According to Pain Score



DISCUSSION

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.[1]. Among adolescents in the Philippines, chronic RHD is the 4th leading cause of mortality, with a mortality rate of 2.9 per 100,000.[15] Early diagnosis, treatment, and secondary prevention with benzathine penicillin G is important to ease the burden of RF and RHD in our country. Compliance to treatment in secondary prevention of RF and RHD is an important aspect in preventing recurrences and complications. Pain and tenderness at site of injection is one of the factors affecting compliance because of the need for repeated injection every 3 weeks. Many centers employ techniques to reduce the pain in IM injections, such as use of smaller gauge needles, direct pressure, slow injections and distractions. [6]

This study compared the pain score after using lidocaine hydrochloride 1% versus sterile water as diluent of BPG, and it demonstrated that BPG injection using lidocaine hydrochloride 1% significantly decreased injection pain; from an average pain score of 4.88, it was significantly decreased to 0.63 ($p<0.0001$).

The result of this study was consistent with the two previous studies done by Amir et al and Morsy et al showing significantly decreased pain score among patients who received BPG diluted in lidocaine hydrochloride 1%.

Lidocaine is one of the most commonly used local anaesthetics. It works by blocking activated and inactivated sodium channels with rapid kinetics. As a local anesthetic, it has an onset of action of 10 minutes, and elimination half-life of 1.6 hours.[7] Four ml of lidocaine hydrochloride 1% was used in this study . In the previous 2 studies, 3.2 mL of lidocaine hydrochloride 1% was used for each patient. Both of these volumes are within the maximum allowable dose of 4.5 mg/kg/dose up to 300mg. [10]

A limitation of this study is that only one injection for BPG diluted in lidocaine hydrochloride 1% and one injection for BPG diluted in sterile water was given to each patient due to time limitation. Multiple injections may give more accurate pain assessment scores post-injection since it will be averaging different injection pain scores at different times.

CONCLUSION AND RECOMMENDATIONS

This study demonstrates that the use of lidocaine hydrochloride 1% as diluent for BPG significantly and safely reduced the injection pain among RF and RHD patients ($p < 0.0001$). No adverse effect was noted among patients in the study. In all patients diagnosed with RF and RHD, BPG injection should be diluted in lidocaine hydrochloride 1%. Implementation of a clinical practice guideline by the Philippine Pediatric Society and Philippine Society of Pediatric Cardiology that will standardize the method of diluting BPG using lidocaine hydrochloride 1% and a study on the improved compliance rate of RF and RHD patients receiving BPG diluted in lidocaine can also be done.

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