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Lidocaine as a Diluent for Benzathine Penicillin G Reduces Injection Pain in Patients with Rheumatic Fever: a Prospective, Randomized Double-Blinded Crossover Study

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Abstract: Benzathine penicillin G (BPG) injection is painful and this may lead to noncompliance with risk of recurrence in rheumatic fever (RF) patients. This study aims to compare the effect of BPG diluted in lidocaine versus that diluted in sterile water on injection pain and serum penicillin levels in patients with rheumatic heart disease (RHD). It is a randomized double blind crossover study that was conducted over 2 months period at 2 hospitals; Sohag University hospital, Egypt and MCH, Madinah, Saudi Arabia. One hundred patients with RHD were divided into 2 groups. The first group received BPG diluted in water for a month then diluted in lidocaine over the next month. The other group received the same schedule in reverse order. Pain was assessed using Faces Pain Scale. Serum penicillin levels were measured microbiologically by agar well diffusion method. There was no statistical significant difference between serum penicillin levels in both groups throughout the whole study period. Immediately after injection, the pain score was significantly less in patients receiving BPG diluted in lidocaine hydrochloride ($p < 0.0001$). We concluded that BPG diluted in lidocaine reduces immediate post injection pain and does not affect serum penicillin levels**.**

Key words: RHD, Heart, penicillin, valve, rheumatic, lidocaine.

INTRODUCTION

Group A beta hemolytic streptocoocal (GABHS) infection is responsible for significant morbidity and mortality in children. The most serious complication of GABHS infection is the development of rheumatic fever (RF) and Rheumatic heart disease (RHD) (Carapetis *et al.*, 2005) A systematic review of 10 population-based studies published from 1967 to 1996 describes the worldwide incidence of RF (Tibazarwa *et al.*, 2008) The highest reported annual incidence rate was 51 per 100,000 per year by a study conducted in northern India, with the mean incidence of all studies at 19 per 100,000 per year. The lowest incidence rates were found in American and Western European nations, while higher rates are found in Eastern Europe, Asia, Australasia, and the Middle East.

Prophylaxis against GABHS is available to prevent recurrent episodes of ARF. An injection of 1 200 000 U of benzathine penicillin G (BPG) preparation every 3- 4 weeks is the recommended regimen for secondary prevention in most circumstances (Gerber *et al.*, 2009). BPG is routinely given diluted in sterile water, but pain of injection leads to non-compliance in some patients with increased risk of recurrence of RF. Lidocaine as a diluent, to decrease pain of injection, had been tried before with some antibiotics as ceftriaxone and proved to be effective in pain reduction (Schichor *et al.*, 1994). Use of lidocaine as a diluent for BPG may lead to pain reduction and improve compliance with decreased incidence of GABHS infection and RF recurrence.

Objectives:

This study aims to compare the effect of BPG diluted in lidocaine hydrochloride 1% versus that diluted in sterile water on injection pain and serum penicillin levels in patients with RHD.

Patients and Methods:

This study was conducted as a randomized double blind crossover trial. The study was conducted over 2 months period; March and April 2011 at 2 hospitals; Sohag University hospital, Sohag, Egypt and Maternity and children hospital, Madinah, Saudi Arabia.

Patients were recruited from the outpatient pediatric cardiology clinic. Inclusion criteria were patients with RHD who are on regular BPG injection. Exclusion criteria were: (1) patients younger than 10 years to avoid

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possible wrong pain score assessment, (2) sensitivity to penicillin or lidocaine. Informed consent to participate in the study was obtained from all patients, parents or relatives. The local ethics committee approved this study

After enrollment, patients were randomly allocated into 2 groups. The first group received 1 200 000 U of BPG diluted in 3.2 ml sterile water in the first month and diluted in 3.2 ml of lidocaine hydrochloride 1% in the second month. The other group received the same regimen but in reverse order with lidocaine hydrochloride first. The physician and patient were kept blind about the randomization. Only the 2 nurses in charge who were responsible for the injection were aware about this randomization. The injections were given intramuscularly in the gluteus muscle.

Throat cultures for Group A beta-hemolytic streptococcai (GABHS) were conducted in all patients immediately before injection and later on after 3 and 4 weeks. Venous blood samples were obtained from each patient for serum penicillin concentration analysis. Blood samples were withdrawn immediately before injection, 24 hours later and then weekly for 4 weeks. The serum was separated and the samples were given specific codes for identification. They were frozen immediately and kept frozen till the time of analysis. The samples were sent to the laboratory for analysis of serum penicillin levels. The serum penicillin levels were measured microbiologically by agar well diffusion method (Lightbrown & Sulitzeanu, 1957). Sarcina lutea ATCC 9341-A was inoculated in agar plates and used as the indicator organism for the penicillin assay. Serum samples were tested in the agar plates inoculated with M. luteus. Zones of inhibition were measured after overnight incubation at 32°C. The sensitivity of the method allowed detection of concentrations as low as 0.003 µg/ml in sera. We expected that some patients will miss some blood withdrawal appointments, so the protocol was to substitute such values by the average of the previous and next samples. This can't be applied to the values immediately before injection but we expect this sample will be available in all patients as they are ready available for BPG injection.

Pain was measured using the revised Faces pain scale (Bieri *et al.*, 1990, Hicks *et al.*, 2001). It is formed of 6 faces representing different stages of painful expression. The faces changed from left "no pain" to the most right "worst Pain". Patient should select a face which represents his sensation of severity of pain. The scale from left to right is 0, 2,4,6,8 and 10.

Statistical Analysis:

Statistical analysis was done using Instat statistical analysis software (GraphPad Software, Inc., CA, USA). Paired t test was used to compare the results between the two groups. P value was set ≤ 0.05.

Results:

One hundred and seventeen patients were eligible for the study. Seventeen patients refused to participate because they were from remote areas and found it difficult to follow the protocol of the study. One hundred patients participated in the study; 57 patient from Saudi Arabia and 43 patients from Egypt. Females were more than males (62:38) and the age was 14.3 ±2.4years (mean ±SD) with a range from 10 to 19 years. Before enrollment, all patients were in regular BPG injection and the last injection was one month ago and was diluted in sterile water. There were some patients who missed appointments of blood withdrawal for assessment of serum penicillin levels. In such cases the missed serum penicillin level was assumed by taking the average of the previous and next serum penicillin level. This was done in 100 serum penicillin levels from the total 1200 levels (8.3%). All serum penicillin levels before injection, day 1 and day 28 were available. The results of serum penicillin level just before BPG injection were not significantly different between both groups. The peak serum penicillin level was noticed in the 24 hour samples and then gradually decreased over the following weeks. By the end of the third and fourth weeks the mean serum penicillin level in both groups was 0.03 µg/ml and 0.017 µg/ml respectively **(figure 1).** There was no statistical significant difference between serum penicillin levels in both groups throughout the whole study period **(table 1).**

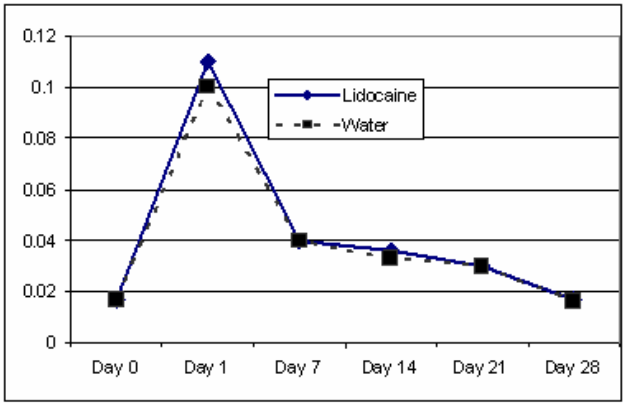

Fig. 1: Time graph representing the serum penicillin levels (µg/ml) before and after BPG injection using lidocaine or water as diluent.

Table 1: Serum penicillin levels (µg/ml) throughout the study period.

Time from injection	Lidocaine diluent	Water diluent	p value
Before injection	0.02 ± (0.02)	0.016 ± (0.01)	0.1
After 24 hours	0.11 ± (0.02)	0.1 ± (0.004)	0.1
After 7 days	0.04 ± (0.01)	0.05 ± (0.01)	0.7
After 14 days	0.036 ± (0.009)	0.033 ± (0.008)	0.7
After 21 days	0.03 ± (0.008)	0.03 ± (0.006)	0.7
After 28 days	0.017 ± (0.005)	0.016 ± (0.006)	0.7

Data is presented as mean ± (SD)

Immediately after injection, the pain score was significantly less in patients receiving BPG diluted in lidocaine hydrochloride. Pain score was 5.2 (range 4 to 8) versus 6.7 (range 4 to 10) with p value < 0.0001. Pain score at 2-4 hours and 24 hours after shows no significant difference between both groups **(figure 2).** Immediately after injection, we noted that patients who received BPG diluted in lidocaine hydrochloride had score pain mainly in the value of 4 and 6 with only 2 patients experienced scale of 8 and none scale of 10. On the other hand 50% of patients who received BPG diluted in water experienced severe pain with scale of 8 or 10 **(figure3).**

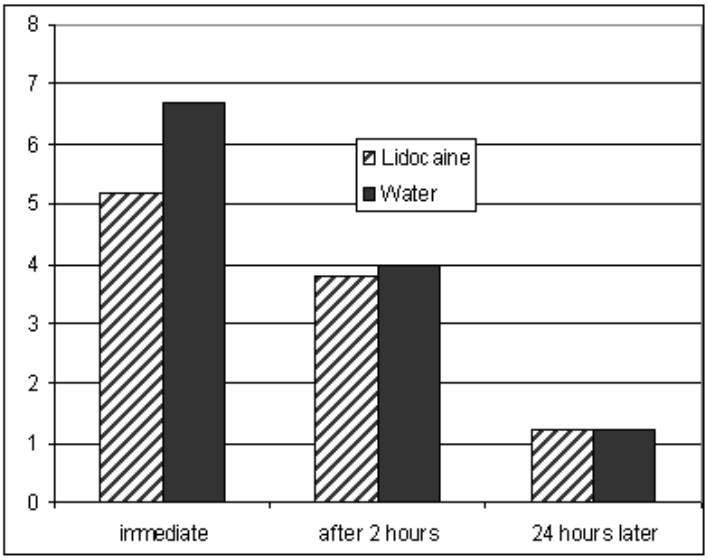

Fig. 2: Pain score in relation to time with either lidocaine or water as diluent for BPG.

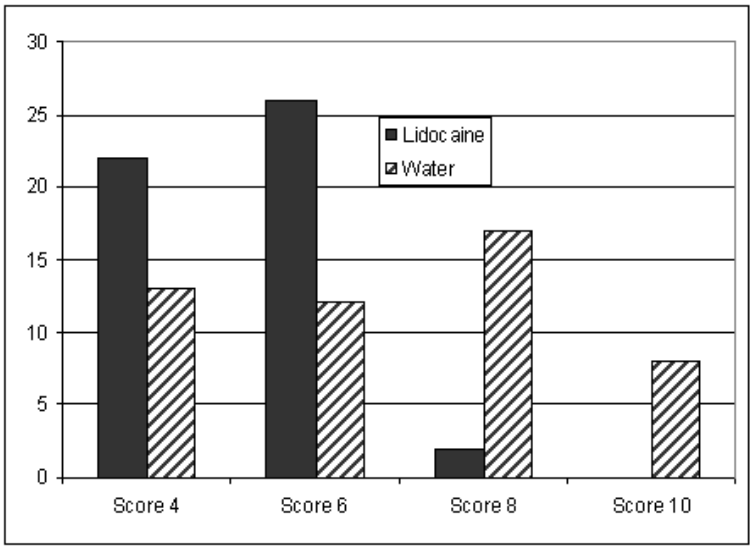

Fig. 3: Stratification of patients according to pain scale showing most of patients with BPG diluted in water were in the high pain scale and the reverse with BPG diluted in lidocaine.

There was no significant difference regarding GABHS between both groups with only 2 positive cultures in the sterile water group and 1 positive culture in the lidocaine group. All were detected in the 4th week throat culture.

Discussion:

Pain during injection of drugs is a common problem both in children and adults. Some previous studies tried different techniques to avoid injection pain. In one study they compared lidocaine patches versus topical benzocaine gel in pain reduction (Kreider *et al.*, 2001) while in another study, the authors compared lidocaine, metoclopramide, and flurbiprofen axetil for reducing pain on injection of propofol (Fujii & Itakura, 2008). In patients with RHD, the problem of BPG injection pain is repeating every 3-4 weeks and so it is of special concern. This study demonstrated that BPG injection using lidocaine hydrochloride 1% reduces injection pain severity. This is the first study to test this technique on a considerably large number of patients with RHD. A previous study using the same technique had a limited number of 18 patients (Amir *et al.*, 1998). We suggested that administration of BPG diluted in lidocaine hydrochloride 1% will decrease injection pain severity which may increase compliance to the drug.

The study also demonstrated that there was no difference in serum penicillin levels with either diluent during the whole month period. This indicated that use of lidocaine as diluent will reduce pain without compromising the desired effect. We used a sensitive bioassay method which could detect serum penicillin level as low as 0.003 μg/ml.(Lightbrown & Sulitzeanu, 1957) This technique is more sensitive than that used in the previous similar study conducted by Amir and associats (1998).

We observed our patients for a possible toxicity from lidocaine. No patients had any sign of toxicity from lidocaine. We used 3.2 ml of lidocaine hydrochloride 1% which equals to 32 mg of lidocaine which is lower than the recommended maximum dose of lidocaine without epinephrine of 4.5 mg/kg.(Physicians's Desk reference, 1992)

A limitation of our study is that we enrolled only patients 10 years or older. This will give us more trust about their expression regarding Facial pain scale, but on the other hand we could not know what will be the results in the younger children 5-10 years old.

Our work revealed that lidocaine as diluent to BPG significantly reduced the pain associated with injection. The lidocaine dose given has no threat of toxic effects and has no impact on serum penicillin level. This will raise a question why we should not use it as diluent of choice for BPG.

Conclusion:

Use of BPG diluted in lidocaine hydrochloride 1% reduces immediate post injection pain and does not change serum penicillin levels. We suggest using lidocaine hydrochloride 1% as diluent of choice for BPG.

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