

# Lidocaine Reducing Pain from Benzathine Penicillin Injection: A Controlled Trial

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## ABSTRACT

**Objective:** This study aimed to investigate the efficacy and safety of benzathine penicillin G (BPG) injection compared between dilution with 1% lidocaine hydrochloride and dilution with sterile water to reduce pain in Thai male syphilis patients.

**Materials and Methods:** This randomized, split-buttock, double-blind controlled trial was conducted at the Sexually Transmitted Disease and HIV Division, Department of Dermatology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand during September 2018 to July 2019. After randomization, 20 left and 20 right buttocks were injected with 1.2 million-unit BPG (half dose) with lidocaine as the diluent. The other 20 left and 20 right buttocks were then injected with 1.2 million-unit BPG (half dose) with sterile water as the diluent. Pain at each buttock was measured by numeric rating scale during and immediately after the injection, and at 5 minutes, 20 minutes, and 24 hours after injection.

**Results:** Forty males (mean age: 30.6±10.3 years) were included. Compared to sterile water diluent, we found that dilution with 1% lidocaine significantly reduced pain during and immediately after injection, and at 5-minutes and 20-minutes post-injection (all  $p < 0.001$ ). There was no significant improvement in pain at 24-hours post-injection. Minor adverse events were observed in 37.5% of patients, including generalized rash, pruritus, and fever. One patient experienced minor drug allergy.

**Conclusion:** One percent lidocaine as a diluent of BPG was found to be effective for reducing pain during and after BPG injection.

**Keywords:** Efficacy; 1% lidocaine hydrochloride; sterile water; pain; benzathine penicillin G injection; syphilis (Siriraj Med J 2022; 74: 699-704)

## INTRODUCTION

Syphilis is a bacterial infectious disease that is caused by *Treponema pallidum* subspecies *pallidum*.<sup>1</sup> Effective treatment is intramuscular (IM) penicillin G for all stages of the disease. In adults, one IM injection of benzathine penicillin G (BPG) 2.4 million units is recommended for early syphilis treatment, including primary, secondary, and early latent syphilis. Three doses (once a week for 3

consecutive weeks) of BPG 2.4 million units is suggested for late latent and tertiary syphilis without neurosyphilis treatment.<sup>1</sup>

BPG that is diluted with sterile water causes pain during and after injection at the injection sites. The local pain and discomfort associated with the injection tend to decrease compliance, especially in children and adolescents.<sup>2,3</sup> To reduce pain and improve patient compliance in those

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requiring 3 injections, we set forth to investigate the efficacy and safety of BPG injection compared between dilution with 1% lidocaine hydrochloride and dilution with sterile water to reduce pain in Thai male syphilis patients.

### MATERIALS AND METHODS

This randomized, split-buttock, double-blind controlled trial in syphilis patients aged 18 years or older was conducted at the Sexually Transmitted Disease and HIV Division of the Department of Dermatology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand during September 2018 to July 2019. Patients with allergy to lidocaine or penicillin were excluded. The protocol for this study was approved by the Siriraj Institutional Review Board (SIRB) (Si 635/2017), and written informed consent was obtained from all study participants.

Both buttocks of each patient were randomized using block randomization with a block size of four. It was used to determine which side of the buttock was intervention or control. Thus, for instance, BPG diluted with lidocaine mean intervention or BPG diluted with sterile water mean control (Fig 1). The dilution was 1.2 million-unit BPG whether with 4.0 ml of lidocaine or with 4.0 ml of sterile water. One dermatologist prepared

medication for administration. However, only the first dose of injection was examined in those required three doses of injection.

A 20-gauge 1.5-inch-long needle was used for injection. One blinded dermatologist performed drug injection at each buttock intramuscularly. All participants were blinded. Pain was assessed using a numeric rating scale, with a zero indicating no pain, and a ten indicating the most severe pain. Pain was assessed during and immediately after the injection, and at 5 minutes, 20 minutes, and 24 hours after the injection. Adverse effects and events were recorded. The same blinded dermatologist assessed pain score and adverse effect.

### Statistical methods

The data were analyzed using Statistical Package for the Social Sciences (SPSS, Inc., Chicago, IL, USA) version 18. Categorical data are reported as number and percentage, and continuous data are reported as mean plus/minus standard deviation. Paired *t*-test was used to compare the pain score between the two diluent formulations at during and immediately after the injection, and at 5 minutes, 20 minutes, and 24 hours after the injection. A *p*-value less than 0.05 was considered statistically significant for all tests.

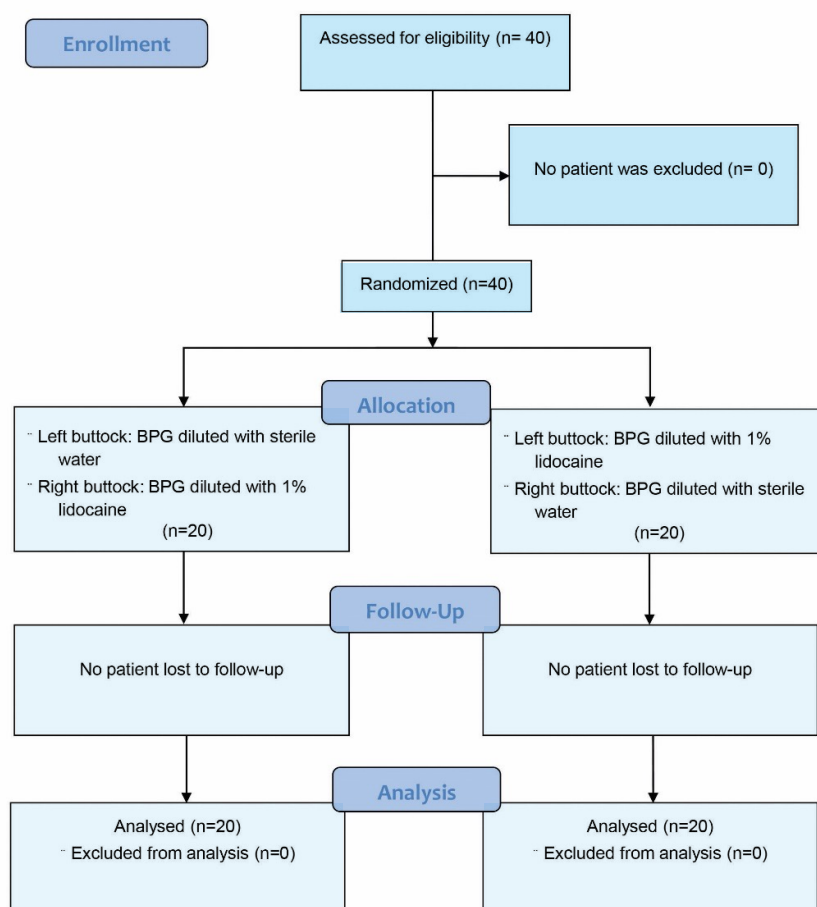
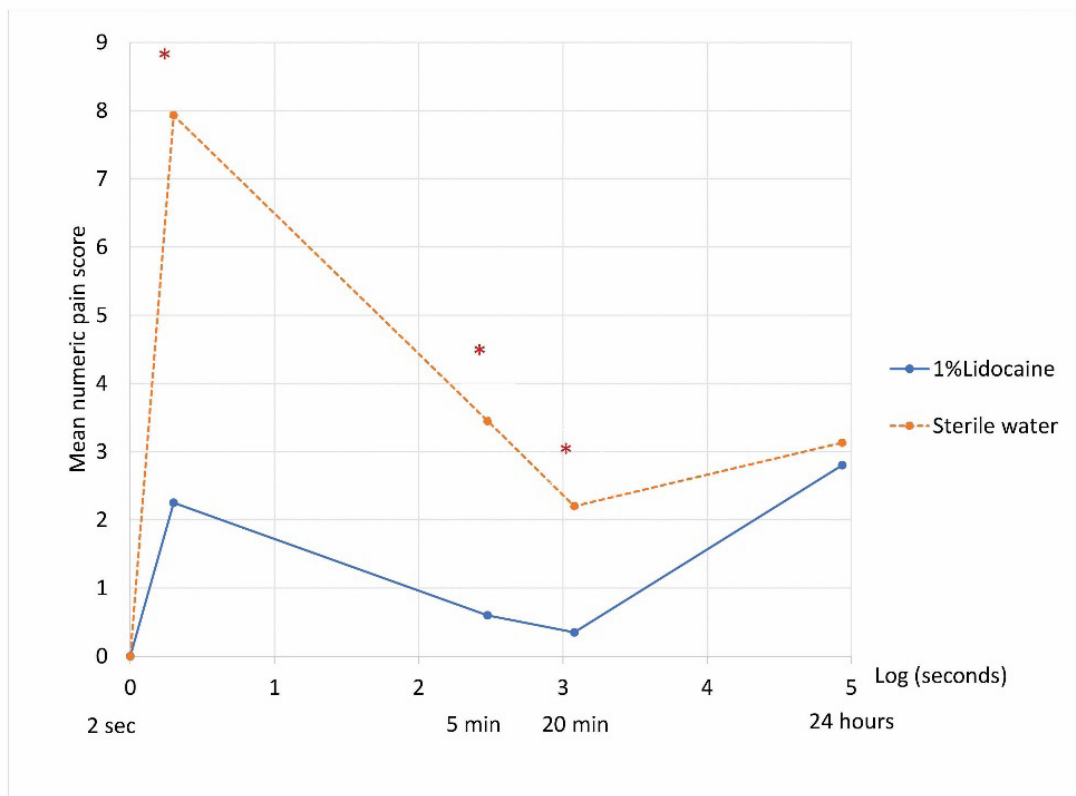


Fig 1. Flow diagram of the randomized clinical trial of benzathine penicillin G (BPG).



**Fig 2.** Mean numeric pain score over time compared between injection of BPG diluted with 1% lidocaine and injection of BPG diluted with sterile water.

## RESULTS

Forty Thai males that were recruited from our outpatient dermatology clinic were included. The age of patients ranged from 18 to 59 years, and the mean age was  $30.6 \pm 10.3$  years. Half of patients reported being homosexual, and 15% were bisexual. No patients reported that they always use a condom during intercourse. Fifty-five and forty percent of patients were in the late latent stage or secondary stage of syphilis, respectively. Thirty-three of 37 patients had a Venereal Disease Research Laboratory (VDRL) titer higher than 1:16, and all patients had a positive *Treponema pallidum* particle agglutination assay (TPHA) result (Table 1). Compared to sterile water diluent, we found that dilution with 1% lidocaine significantly reduced pain during and immediately after injection, and at 5-minutes and 20-minutes post-injection (all  $p < 0.001$ ) (Table 2). There was no significant improvement in pain at 24-hours post-injection. Minor adverse events were observed in 37.5% of patients, including generalized rash, pruritus, and fever. One patient experienced minor drug allergy (Table 3). However, there was no local adverse event so the local adverse event between study and control group could not done.

## DISCUSSION

Our study showed that BPG injection using 1% lidocaine as the diluent significantly reduces pain at injection sites during and immediately after the injection, and at 5 minutes and 20 minutes after the injection. Interestingly, however, the pain score in the lidocaine group increased by the 24-hour time point to very near the pain score in the sterile water group. This study also found intramuscular injection with BPG to be associated with two distinct episodes of pain during and immediately after injection, and at 24 hours after injection. This reemergence of pain after a decrease in pain at 5-minutes and 20-minutes post-injection is likely due to the fact that the elimination half-life of lidocaine is biphasic within a range of 90-120 minutes in most patients.<sup>4</sup>

Pain during intramuscular injection is a problem in clinical practice.<sup>5</sup> Reducing intramuscular injection pain may be achieved by combining drugs with local anesthetics, such as lidocaine.<sup>6</sup> Lidocaine is a sodium-channel blocking drug with rapid onset of action, and it has a minimal toxicity profile.<sup>2,7</sup> Four milliliters of 1% lidocaine was used in this study for a total dose of 2 mg. This is less than the maximum dose of lidocaine without

**TABLE 1.** Demographic and clinical characteristics of the 40 included syphilis patients.

Characteristics	n	%
Age (years)		
Mean ± SD	30.6 ± 10.3	-
Range	18-59	-
Sexual orientation		
Homosexual	20	50.0
Heterosexual	14	35.0
Bisexual	6	15.0
Frequency of condom use		
Always	0	0.0
Sometimes	37	92.5
Never	3	7.5
Underlying medical condition		
Yes	7	17.5
No	33	82.5
HIV infection	23	57.5
Stage of syphilis		
Primary syphilis	0	0.0
Secondary syphilis	16	40.0
Early latent syphilis	2	5.0
Late latent syphilis	22	55.0
Tertiary Syphilis	0	0.0
Presence history of known contact disease	11	30.8
Recurrent syphilis	9	19.2
TPHA reactive at diagnosis (titer)	38	100.0
>1:80	38	100.0
VDRL reactive at diagnosis (titer)	37	92.5
1:1	2	5.4
1:2	1	2.7
1:4	1	2.7
1:16	3	8.1
1:32	7	18.9
1:64	8	21.6
1:128	11	29.7
1:256	4	10.8

**TABLE 2.** Mean pain visual analogue scale (VAS) at different time points compared between injection of benzathine penicillin G diluted with 1% lidocaine and injection of benzathine penicillin G diluted with sterile water.

	1% Lidocaine side (mean±SD)	Sterile water side (mean±SD)	P-value
During and immediately after injection	2.25±1.85	7.93±1.95	<b>1.45 x 10<sup>-18*</sup></b>
5 minutes after injection	0.60±1.43	3.45±2.64	<b>4.55 x 10<sup>-8*</sup></b>
20 minutes after injection	0.35±1.21	2.20±2.15	<b>7.12 x 10<sup>-6*</sup></b>
24 hours after injection	2.80±1.94	3.13±2.08	0.156

\*A p-value<0.05 indicates statistical significance

**TABLE 3.** Adverse events and complication at 24 hours after treatment among the 40 included syphilis patients.

Adverse events and complication	n	(%)
<b>Adverse events</b>		
No	25	62.5%
Yes	15	37.5%
Generalized rash	9	60.0%
Generalized pruritus	8	53.3%
Fever	8	53.3%
<b>Complication</b>		
No	39	97.5%
Yes	1	2.5%
Minor drug allergy	1	100.0%

epinephrine, which was reported to be 300 mg.<sup>8</sup> All patients in this study were observed for lidocaine toxicity, and no signs of toxicity were observed. Previous studies reported no adverse pharmacokinetic effects of lidocaine on IM penicillin.<sup>2,9</sup> It was also reported that the BPG combined with lidocaine did not change the concentration of penicillin in body fluid.<sup>2</sup> No local adverse event was observed in our study. The adverse events in our study were generalized symptoms such as rash, pruritus, and fever. Because participants received both interventions and all of them had no history of allergy from penicillin<sup>10</sup> or lidocaine<sup>11</sup>, so these recorded generalized symptoms might be from penicillin or lidocaine.

## CONCLUSION

One percent lidocaine as a diluent of BPG was found to be effective for significantly reducing pain during and immediately after BPG injection, and at 5-minutes and 20-minutes post-injection. We recommend the use of 1% lidocaine as a diluent for BPG in this clinical setting.

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**Conflict of interest:** All authors declare they have no personal or professional conflicts of interest relating to any aspect of this study.

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