Original Article

# A Double-Blind, Randomised, Placebo-Controlled Trial of EMLA® Cream (Eutectic Lidocaine/Prilocaine Cream) for Analgesia Prior to Cryotherapy of Plantar Warts in Adults

Siew Hui Lee, [1]*MSN, BSN, CCN,* Janthorn Pakdeethai, [2,3]*MBBS (Melbourne), MRCP(UK), MMed (Int Med)*, Matthias PHS Toh, [4,5]*MBBS, MMed (Public Health), FAMS,* Derrick CW Aw, [2,3]*MRCP(UK), FAMS, GDA*

## Abstract

**Introduction: Cryotherapy with liquid nitrogen is an effective, safe and convenient form of treatment for plantar warts. EMLA® cream (eutectic mixture of lidocaine 2.5% and prilocaine 2.5%) is a topical local anaesthetic agent that has proven to be effective and well tolerated in the relief of pain associated with various minor interventions in numerous clinical settings. Materials and Methods: In a single-centre, double-blind, randomised placebo-controlled study, 64 subjects were randomised into 2 groups. The subjects had a thick layer of EMLA® cream or placebo cream applied to pared plantar wart(s) and onto the surrounding margin of 1 mm to 2 mm under occlusion for 60 minutes prior to receiving cryotherapy. The pain of cryotherapy was evaluated by the subjects using a self-administered Visual Analogue Scale (VAS) immediately after the cryotherapy. Results: There was no statistical difference between the mean VAS score for EMLA® cream (47.0 ± 21.4 mm) and placebo (48.9 ± 22.0 mm). Those with more than 1 wart had a significantly higher VAS score than those with only 1 wart (59.1 ± 21.8 vs. 44.3 ± 20.4, *P* <0.05) but this did not affect the therapeutic effect of EMLA® cream prior to cryotherapy. Conclusion: We conclude that the application of EMLA® cream prior to cryotherapy does not reduce the pain associated with cryotherapy.**

**Ann Acad Med Singapore 2014;43:511-4**

**Key words: Anaesthetic, Pain, Wart**

## Introduction

Plantar warts are commonly diagnosed in dermatology clinics. They are painful, contagious and have the potential to cause considerable morbidity.[1] Among the therapeutic modalities, cryotherapy with liquid nitrogen is an effective, safe and convenient form of treatment for plantar warts.[2] However, therapeutic doses of liquid nitrogen can produce pain caused by the stinging sensation and the inflammation during the freezing cycle. It is not unbearable and usually short-lived. The wart will begin to turn white; this is a sign that the skin cells are dying. A blister may also form at the site of the wart. It is important to leave the blister alone; it will heal within a week.

EMLA® cream (eutectic mixture of lidocaine 2.5% and prilocaine 2.5%), a topical local anaesthetic agent has proven to be effective and well tolerated in the relief of pain associated with various minor interventions in numerous clinical settings.[3-8] In the dermatology setting, studies on the effect of EMLA® cream to anaesthetise warts before cryotherapy were mainly confined to warts on non-hardened skin.[9,10]

In a comparative study of children and adults, Gupta et al[11] found that EMLA® cream reduced pain over hardened skin (palms and soles) in children. To our knowledge, there have been no studies looking at the effectiveness of EMLA® cream to anaesthetise pared warts for liquid nitrogen cryotherapy in adults.

Our study aims to determine whether the application of EMLA® cream prior to cryotherapy could reduce the pain induced by cryotherapy.

[1]Clinical Nursing Unit, National University Hospital, Singapore
[2]Division of Dermatology, Department of Medicine, National University Hospital, Singapore
[3]Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore
[4]Saw Swee Hock School of Public Health, National University of Singapore and National University Health System, Singapore
[5]Information Management, Corporate Development, National Healthcare Group, Singapore
Address for Correspondence: Dr Janthorn Pakdeethai, Division of Dermatology, Department of Medicine, National University Hospital, NUHS Tower Block, Level 10, Singapore 119228.
Email: janthorn_pakdeethai@nuhs.edu.sg

## Materials and Methods

### *Study Design*

The design was a single-centre, double-blind, randomised, placebo-controlled study on a single visit conducted in University Dermatology Clinic, National University Hospital of Singapore. Approval for the study was obtained from the national ethics committee.

### *Patient Selection*

Patients with plantar warts for liquid nitrogen cryotherapy were potential candidates for the study. For inclusion into the study, the patient had to be at least 18 years old and capable of assessing pain using a visual analogue scale (VAS).[12] Both new and follow-up patient were eligible for the study as partially treated warts do not result in less pain caused by the mechanism of cold liquid nitrogen. Patients who had previously used EMLA® cream for cryotherapy of warts, known allergic sensitivity to EMLA® cream or amide type of local anaesthetic or with peripheral sensory neuropathy of both lower limbs were excluded from the study.

The primary outcome of the study was to explore the effect of EMLA® cream on levels of pain in adult patients with pared plantar warts receiving cryotherapy. The power of the study was estimated based on the primary outcome measure of VAS. In order to detect a difference of 25 mm in the pain scored on the VAS, assuming a standard deviation of 30 mm, 32 patients for each treatment arm could achieve 90% power at 5% level of significance.[13]

The subjects were randomly allocated by a computer-generated randomisation sequence into EMLA® cream or placebo group. Physiogel™ cream was chosen as placebo as it was a conveniently available emollient most similar in colour and texture to EMLA® cream. It does not contain local anaesthetics. The assignments of subjects were concealed in sealed opaque envelopes. The randomisation codes and numbers were kept by a laboratory technician at the clinic. Both the subjects and the investigators were masked to group assignment. The randomisation code was unmasked at the end of the study by an assigned statistician.

Using a sharp blade, an investigator pared down the plantar warts of subjects till the texture of the lesion was as soft as the surrounding skin. A designated dermatology technician applied EMLA® cream or placebo cream as a thick layer to the warts and onto the surrounding margin of 1 to 2 mm. A transparent film dressing (Tegaderm™ Film) was applied for 60 minutes. The cream was then removed and liquid nitrogen was applied for 5 to 10 seconds with double freeze-thaw cycles. The end-point of each freeze was a complete ice-ball covering the lesion with 1 to 2 mm peripheral extension. No oral analgesic was allowed prior to cryotherapy.

### *Assessment*

Pain was evaluated using a self-administered VAS immediately after cryotherapy. The subjects were asked to mark their level of pain experienced during cryotherapy on a line from 0 to 100 mm. A score at 0 mm indicates no pain and 100 mm the most severe level of pain.

### *Statistical Methods*

The data were analysed using PASW (version 19.0). Significance testing of proportions was carried out using chi-square test, and of means using t-test and analysis of variance (ANOVA), where a probability ($P$) of less than 0.05 was considered significant.

## Results

A total of 41 male (64%) and 23 female (34%) patients were enrolled. The EMLA® cream and placebo groups were comparable with regard to age, gender and race (Table 1). Out of the 64 patients, 48 (75%) patients had 1 wart and the rest had more than 1 wart. The mean duration of wart in the EMLA® cream and placebo groups were 7.7 ± 1.9 and 7.9 ± 2.1 months respectively, and the mean size of the wart were 7.0 ± 4.3 mm and 6.7 ± 2.8 mm respectively. The majority (78.1%) had warts smaller than 10 mm in diameter.

The mean VAS score for EMLA® cream was 47.0 ± 21.4 mm and the placebo was 48.9 ± 22 mm. There was no statistical difference in the VAS score of cryotherapy between the 2 groups (Table 2). Analysis by gender showed the mean scores for men in the EMLA® cream and placebo groups to be 47.4 ± 21.7 and 46.0 ± 21.9 and female to be 46.4 ± 21.9 and 53.8 ± 21.9 respectively. There were no statistical differences in VAS scores between gender, duration and size of warts.

Younger non-Chinese participants, however, had a high mean VAS scores (51.2 ± 23 for age <25 years vs. 43.8 ± 19.4 mm for ≥25 years, $P$ <0.05; and 51.5 ± 21.4 for non-Chinese vs. 44.0 ± 21.4 mm for Chinese, $P$ <0.05). This is non-significant and can be due to the small sample size. There was a statistically significant difference in the mean VAS scores of patients with only 1 and more than 1 wart (44.3 ± 20.4 vs. 59.1 ± 21.8 mm, $P$ <0.05). This did not affect the conclusion regarding therapeutic effect of EMLA® cream prior to cryotherapy.

## Discussion

Our study demonstrates that the application of EMLA® cream prior to cryotherapy to plantar warts does not reduce the pain associated with cryotherapy. The time and cost of EMLA® cream application may negate the statistically non-significant pain reduction during the treatment process. This

Table 1. Demographic Characteristics of the Study Population

| Characteristics | | Total (n = 64) | | EMLA (n = 32) | | Placebo (n = 32) | |
|---|---|---|---|---|---|---|---|
| | | Number | % | Number | Row % | Number | Row % |
| Age (years) | <20 | 14 | 21.9 | 7 | 50.0 | 7 | 50.0 |
| | 21 – 30 | 26 | 40.6 | 15 | 42.3 | 11 | 57.7 |
| | 31 – 40 | 5 | 7.8 | 1 | 20.0 | 4 | 80.0 |
| | 41 – 50 | 6 | 9.4 | 2 | 33.3 | 4 | 61.7 |
| | 51 – 60 | 11 | 17.2 | 6 | 54.5 | 5 | 45.5 |
| | 61 and above | 2 | 3.1 | 1 | 50.0 | 1 | 50.0 |
| | mean ± SD | 31.9 ± 14.9 | | 31.4 ± 15.1 | | 32.3 ± 14.9 | |
| Gender | Male | 41 | 61.1 | 21 | 51.2 | 20 | 48.8 |
| | Female | 23 | 35.9 | 11 | 47.8 | 12 | 52.2 |
| Ethnicity | Chinese | 30 | 46.9 | 13 | 43.3 | 17 | 56.7 |
| | Non-Chinese | 34 | 53.1 | 19 | 55.9 | 15 | 44.1 |
| Number of warts | 1 | 48 | 75.0 | 23 | 47.9 | 25 | 52.1 |
| | 2 or more | 16 | 25.0 | 9 | 56.0 | 7 | 43.8 |
| Size of warts (mm) | Less than 5 | 19 | 29.7 | 10 | 52.6 | 9 | 47.4 |
| | 5 – 9 | 31 | 48.4 | 14 | 45.2 | 17 | 54.8 |
| | 10 or more | 14 | 21.9 | 8 | 57.1 | 6 | 42.9 |
| | mean ± SD | 6.9 ± 3.6 | | 7.0 ± 4.3 | | 6.7 ± 2.8 | |
| Duration of warts (months) | Less than 6 | 36 | 56.3 | 18 | 56.3 | 18 | 56.3 |
| | 6 – 11 | 10 | 15.6 | 3 | 9.4 | 7 | 21.9 |
| | More than 12 | 18 | 28.1 | 11 | 34.4 | 7 | 21.9 |
| | mean ± SD | 7.8 ± 1.4 | | 7.7 ± 1.9 | | 7.9 ± 2.1 | |

EMLA®: Eutectic mixture of lidocaine and prilocaine

Table 2. VAS Scores by Treatment Group

| | | Total (n = 64) | *P* value | EMLA [A] (n = 32) | Placebo [B] (n = 32) | *P* value [A] vs [B] |
|---|---|---|---|---|---|---|
| VAS | mean ± SD | 48.0 ± 21.6 | | 47.0 ± 21.4 | 48.9 ± 22.0 | NS |
| Gender | Male | 46.7 ± 21.6 | NS | 47.4 ± 21.7 | 46.0 ± 22.1 | NS |
| | Female | 50.2 ± 21.7 | | 46.4 ± 21.9 | 53.8 ± 21.9 | NS |
| Age Group (years) | Below 25 | 51.2 ± 23.0 | NS | 50.6 ± 21.8 | 54.0 ± 25.0 | NS |
| | 25 and above | 43.8 ± 19.4 | | 43.0 ± 21.0 | 44.4 ± 18.5 | NS |
| Ethnicity | Chinese | 44.0 ± 21.4 | NS | 41.2 ± 20.4 | 46.2 ± 22.5 | NS |
| | Non-Chinese | 51.5 ± 21.4 | | 51.1 ± 21.7 | 52.0 ± 21.8 | NS |
| Number of warts | 1 | 44.3 ± 20.4 | <0.05 | 45.2 ± 21.8 | 43.4 ± 19.4 | NS |
| | 2 or more | 59.1 ± 21.8 | | 51.7 ± 20.9 | 68.6 ± 20.6 | NS |
| Size of warts (mm) | Less than 5 | 49.7 ± 17.4 | NS | 50.0 ± 16.0 | 49.4 ± 19.9 | NS |
| | 5 – 9 | 50.8 ± 24.9 | | 50.0 ± 27.0 | 51.5 ± 23.9 | NS |
| | 10 or more | 39.3 ± 17.2 | | 38.1 ± 15.3 | 40.8 ± 20.8 | NS |
| Duration of warts (month) | Less than 6 | 47.2 ± 23.5 | NS | 47.8 ± 23.4 | 46.7 ± 24.2 | NS |
| | 6 – 11 | 43.0 ± 20.8 | | 35.0 ± 5.0 | 46.4 ± 24.4 | NS |
| | 12 or more | 52.2 ± 18.0 | | 49.1 ± 21.0 | 57.1 ± 11.9 | NS |

NS: Not significant; EMLA®: Eutectic mixture of lidocaine and prilocaine; VAS: Visual Analogue Scale

finding is in contrast to earlier studies. We postulate that the highly keratotic nature of plantar warts does not allow sufficient penetration of epicutaneously applied EMLA® cream despite pre-treatment paring. Based on the available evidence to date, EMLA® cream is likely an effective topical analgesia used to reduce pain in non-hardened, non-hyperkeratotic skin other than the palms and soles.

This study suggests sex differences in pain perception of cryotherapy. Women tend to have a lower pain threshold than men following the administration of cryotherapy. This may be associated with hyperalgesia in women and hypoactivity of the inhibitory system of pain in females.[14] There are also sex differences in pain relieving effects of EMLA® cream. The poorer response of pain reduction following application of EMLA® cream in males could be the result of a thicker stratum corneum in males.[15]

The only significant finding from this study was that a lower pain threshold was observed in subjects with more than 1 wart. One would be more aggressive with pain control measures when using cryotherapy for patients with more than 1 wart.

Future studies can focus on alternative sites (non-palmoplantar), longer duration of EMLA® cream application, liposome-encapsulated lidocaine, a different topical local anaesthetic and a larger sample size.

## Conclusion

The application of EMLA® cream prior to cryotherapy has no added benefit for reducing pain associated with cryotherapy. Other methods for achieving topical anaesthesia in cryotherapy of plantar warts should be explored.

***Acknowledgements***

*The authors would like to thank the late Dr Teoh Chee Wei, Mdm Peh Bee Eng and all clinic assistants of University Dermatology Clinic for their technical assistance with the conduct of this trial.*

REFERENCES

1. Ciconte A, Campbell J, Tabrizi S, Garland S, Marks R. Warts are not merely blemishes on the skin: A study on the morbidity associated with having viral cutaneous warts. Australas J Dermatol 2003;44:169-73.
2. Buckley D. Cryosurgery treatment of plantar warts. Ir Med J 2000;93: 140-3.
3. Akan A, Eryavuz Y, Kamali S, Simşek S, Hot S, Bademci R. A randomized, placebo controlled study: EMLA in minor breast surgery. Minerva Chir 2012;67:181-5.
4. Buckley MM, Benfield P. Eutectic lidocaine/prilocaine cream. A review of the topical anaesthetic/analgesic efficacy of a eutectic mixture of local anaesthetics (EMLA). Drugs 1993;46:126-51.
5. Fransson J, Rönnerfält L, Wahlgren C F. EMLA cream provides rapid pain relief for the curettage of molluscum contagiosum in children with atopic dermatitis without causing serious application-site reactions. Pediatr Dermatol 1998;15:309-12.
6. Hallin A, Ljunghall K, Wallin J. Topical anaesthesia with local anaesthetic (lidocaine and prilocaine, EMLA) cream for cautery of genital warts. Genitourin Med 1987;63:316-19.
7. Monsonego J, Semaille C. Local anaesthesia of genital mucosa with a lidocaine/prilocaine combination cream before laser therapy of human papillomavirus lesions. Eur J Dermatol 2000;10:607-10.
8. Manner T, Kanto J, Iisalo E, Lindberg R, Viinamäki O, Scheinin M. Reduction of pain at venous cannulation in children with a eutectic mixture of lidocaine and prilocaine (EMLA cream): comparison with placebo cream and no local premedication. Acta Anaesthesiol Scand 1987;31:735-9.
9. Menter A, Black-Noller G, Riendeau LA, Monti KL. The use of EMLA cream and 1% lidocaine infiltration in men for relief of pain associated with the removal of genital warts by cryotherapy. J Am Acad Dermatol 1997;37:96-100.
10. Mansell-Gregory M, Romanowski B. Randomised double blind trial of EMLA for the control of pain related to cryotherapy in the treatment of genital HPV lesions. Sex Transm Infect 1998;74:274-5.
11. Gupta AK, Koren G, Shear NH. A double-blind, randomized, placebo-controlled trial of eutectic lidocaine/prilocaine cream 5% (EMLA) for analgesia prior to cryotherapy of warts in children and adults. Pediatr Dermatol 1998;15:129-33.
12. Tamiya N, Araki S, Ohi G, Inagaki K, Urano N, Hirano W, et al. Assessment of pain, depression, and anxiety by visual analogue scale in Japanese women with rheumatoid arthritis. Scand J Caring Sci 2002;16;137-41.
13. Chan YH. Randomised controlled trials (RCTs) – sample size: the magic number? Singapore Med J 2003;44:172-4.
14. Palmeira CC, Ashmawi HA, Posso Ide P. Sex and Pain Perception and Analgesia. Rev Bras Anestesiol 2011;61;814-28.
15. Sandby-Møller J, Poulsen T, Wulf HC. Epidermal thickness at different body sites: relationship to age, gender, pigmentation, blood content, skin type and smoking habits. Acta Derm Venereol 2003;83:410-3.