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Original Article

Is 5% EMLA an Effective Topical Anesthetic Agent for Replacing Intravenous Pethidine for Extracorporeal Shock Wave Lithotripsy in Patients with Renal or Upper Ureteric Calculi?

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Abstract

Background: **Patients with renal or upper ureteric calculi may require extracorporeal shock wave lithotripsy (ESWL). To suppress the pain during the lithotripsy, commonly used medications included opioids, which give satisfactory analgesia but have numerous side effects.**

Objective: **This study was to determine whether 5% EMLA cream (a topical anesthetic agent) is an adequate analgesic for the lithotripsy, helping to reduce the use and side effects of opioid analgesics.**

Materials and Methods: **The study was a prospective, controlled, randomized, double-blind study. Patients were randomly assigned to either one of two groups (A, B) of 100 patients each. Groups A and B were treated with 5% EMLA and placebo cream, respectively.**

Results: **Both groups were comparable in terms of demographic data, gender, age, body mass index (BMI), site and size of the stones, American Society of Anesthesiologists physical status (ASA class) and comorbidities. The location or point of exposure of sound wave, duration and the number of lithotripsy shock waves were the same in both groups. Numerical rating scale (NRS) was used in the pain assessment. The pain score during the lithotripsy in the 5% EMLA group was found to be significantly lower than that in the control group. The amount of opioid (pethidine) used in the control group was significantly greater. The number of hospitalization hours following the lithotripsy in the control group was significantly higher. Significantly more patients in the control groups experienced dizziness, nausea and headache from intravenous (IV) opioids.**

Conclusion: **The 5% EMLA cream may be used to suppress the pain induced by the renal or upper ureteric lithotripsy and may help reduce opioid use, decreasing opioid-related side effects and hospitalization time.**

Keywords: **lithotripsy, NRS, EMLA, pethidine**

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Introduction

Extracorporeal shock wave lithotripsy (ESWL) is the most common and gold standard treatment of calculi in the urinary tract (kidneys and ureters) indicated for this approach[1,2]. Pain from the ESWL is mainly is parietal pain[3], which is caused by the continuous impacts of ultrasonic shock wave on cutaneous nociceptors, as well as visceral pain (visceral nociceptors), which is caused by the added intrapelvic pressure and the renal capsule distension[4]. Factors influencing ESWL pain include the type of lithotripters, the site and size of the stones and the pressure of shock waves. Anesthesia used may be general, regional or local.

The most commonly used analgesics during the ESWL are opioids, followed by sedatives, non-steroidal anti-inflammatory drugs (NSAIDs) and topical anesthetic creams. Opioids are frequently used, with satisfactory analgesia. A disadvantage of this drug group, however, is its side effects, ranging from light headedness, dizziness, nausea and vomiting todyspnea, respiratory suppression, necessitating treatment and patient monitoring for some time following the lithotripsy. Some patients may even require hospitalization.

5% EMLAcream is a topical anesthetic. It contains 2.5% lidocaine (acetamide, 2-(diethylamino)-N-(2,6-dimethylphenyl)) and 2.5% prilocaine (propanamide, N-(2-methylphenyl)-2-(propylamino)). One gm of 5% EMLA contains 25 mg lidocaine and 25 mg prilocaine. The mechanism of action is stabilization of neuronal membranes by inhibiting the ionic fluxes essential for nerve impulse initiation and conduction, thus producing local anesthesia. The cream penetrates approximately 4 mm into the skin, has an onset time at approximately 10 to 20 minutes, and a duration of action of 60 minutes[5].

The onset, depth and duration of action of EMLA depend on the duration of its exposure prior to surgery, and exposure time will vary according type of surgery. Operations on the genital mucosa usually require 5 to 10 minutes of exposure, while IV opening and split-thickness skin graft require approximately 1 and 2 hours, respectively, of exposure. EMLA is minimally absorbed and hence has little systemic effect (Table 1). It is very safe regardless of how much and for how long it is applied to the skin, even for young patients (Table 2).

Patients and Methods

From January 2016 to March 2017, patients who had renal and upper ureteric calculi with indications for ESWL at Lerdsin Hospital were enrolled into a double-blinded randomized controlled trial to determine whether the EMLA5% cream could be used to replace an opioid analgesic (pethidine) during renal or upper ureteric ESWL, and whether the cream could help reduce the quantity as well as side effects of opioid use. The Hospital's research ethics committee approved the study.

Patients were excluded if any of the following conditions was present: Hypersensitivity to the EMLA 5% cream or opioids (pethidine); obesity (BMI> 30 kg/m^2); active urinary tract infection (UTI); coagulopathy (medical bleeding); pregnancy or nursing mother; uncontrolled hypertension (HT); currently using neuropsychiatric or cardiovascular medications. In addition, patients must refrained from the use of sedatives-hypnotics and antiemetic drugs prior to the lithotripsy.

Patients in the study were randomized into two groups, A and B. Group A received 2 gm of 5% EMLA cream applied at a pre-marked site (by a local technician at the lithotripter), which was the location where the sound waves were to pass to disintegrate the stones. The cream was applied within a10 cm^2 area, covered with occlusive dressing, and left in place for 1 hour prior to lithotripsy. Group B received a placebo cream, which looked identical to the EMLA cream and packaged in similar tubes, but did not contain any anesthetic. The placebo cream was applied in the same way as that in Group A (Figure1).

Data on the age, gender, weight, height, ASA status, underlying diseases, size and site of the stones were recorded for all patients. The lithotripter used was a Dornier-R lithotripter SII (Germany). Lithotripsy steps, intensity, rate and timing were the same in all patients.

Prior to the lithotripsy, pain scores were evaluated by a nurse anesthetist, using a numerical rating system (NRS). Pain scores prior to the procedure must be 2 or less. Vital signs and oxygen saturation were monitored throughout the ESWL.

During the ESWL, pain scores (NRS) and side effects were evaluated every 15 minutes (15, 30 and 45 minutes) after the beginning until the end of the 1 hour lithotripsy. If the pain score was5 or greater, 25

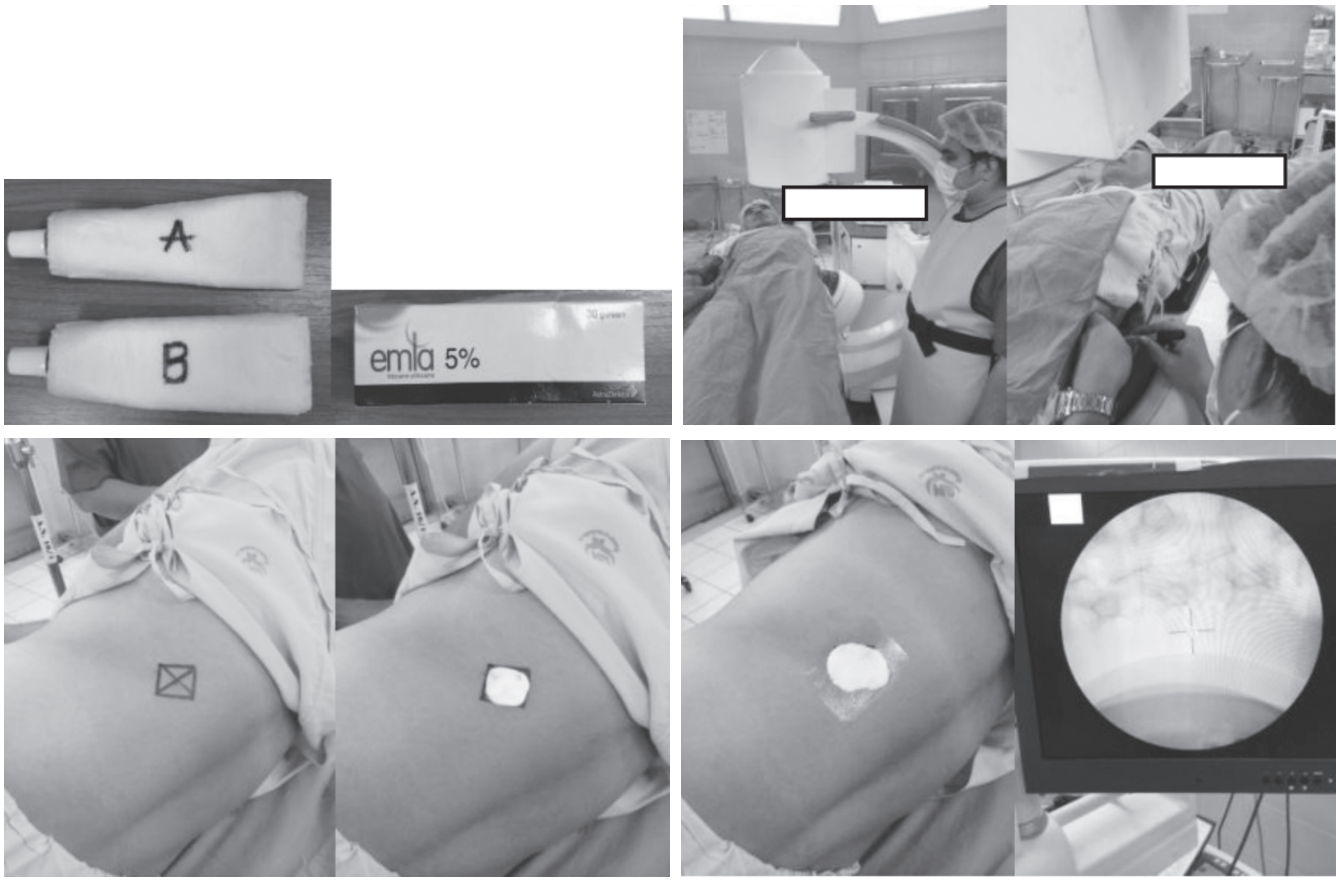

Figure 1 The application of analgesic cream

mg of pethidine was administered intravenously. If patients experienced side effects of pethidine, the usual standard treatment was given.

After the lithotripsy, patients who received intravenous pethidine were observed for a minimum of two hours at the Hospital. Patients who did not receive pethidine could return home as soon as the lithotripsy was finished.

Results

A total of200 patients were recruited into the study, 100 patients to group A with 5% EMLA, and the other 100 to group B with placebo. Table 3 shows the baseline data of the patients. The age, gender, BMI, ASA class, comorbidities, site and size of the stones, the number of shock waves were not significantly different between both groups.

Table 4 shows the pain scores prior to (0 minutes) and at the first (15 minutes), second (30 minutes) and third (45 minutes) time points during lithotripsy. Group A, which received the 5% EMLA, had significantly lower pain scores than group B in all evaluations at 15, 30 and 45 minutes. Table 5 shows the number of patients who received intravenous pethidine in both groups at the first, second and third evaluations. The number of patients receiving intravenous pethidine was significantly fewer in group A than that in group B at 15, 30 and 45 minutes. No patient in group A stayed in the hospital for longer than 2 hours. In group B, 47 patients stayed in the hospital for longer than 2 hours, with one patient staying for 22 hours.

Table 6 shows the number of patients experiencing side effects of intravenous pethidine during lithotripsy. Patients in group A had significantly less nausea, dizziness and headache than those in group B.

Discussion

Patients undergoing ESWL for renal or ureteric calculi often require some form of analgesia, commonly opioids. However, opioids have many side effects

Table 1 Absorption of lidocaine and prilocaine from EMLA cream: normal volunteers (n = 16)

EMLA cream (gm)	Area (cm^2)	Time on (hr)	Drug content (mg)	Absorbed (mg)	C_{max} (μg/mL)	T_{max} (hr)
60	400	3	Lidocaine 1,500	54	0.12	4
			Prilocaine 1,500	92	0.07	4
60	400	24*	Lidocaine 1,500	243	0.28	10
			Prilocaine 1,500	503	0.14	10

*Maximum recommended duration of exposure is 4 hours.

Reference: EMLA - FDA prescribing information, side effects and use; https://www.drugs.com/pro/emla.html

Table 2 Maximum recommended dose and application and time for the EMLA cream by age and weight for infants and children based on application to intact skin

Age and body weight requirements	Maximum total dose of EMLA cream	Maximum application area	Maximum application time
0 up to 3 months or < 5 kg	1 g	10 cm^2	1 hr
3 up to 12 months and > 5 kg	2 g	20 cm^2	4 hr
1 to 6 years and > 10 kg	10 g	100 cm^2	4 hr
7 to 12 years and > 20 kg	20 g	200 cm^2	4 hr

Reference: EMLA - FDA prescribing information, side effects and use; https://www.drugs.com/pro/emla.html

Table 3 Baseline data of the patients in the study

	Placebo (n = 100)	5% EMLA (n = 100)	*p*-value
Number			
Gender			0.622
Male	74	77	
Female	26	23	
ASA class			0.671
Class I	46	49	
Class II	54	51	
Side			0.671
Left	51	48	
Right	49	52	
Type			0.669
Ureteric calculi (UC)	58	55	
Renal calculi (RC)	42	45	
Mean ± SD (range)			
Size of stone (cm)	0.9 ± 0.3 (0.5, 2.0)	0.9 ± 0.3 (0.5, 1.8)	0.349
Age (years)	44.0 ± 11.6 (22, 68)	44.2 ± 10.6 (26, 70)	0.874
Number of shock waves	6904.27 ± 95.25 (6680, 7115)	6893.71 ± 109.36 (6875, 7200)	0.467
BMI	22.9 ± 1.9 (19.05, 27.7)	22.9 ± 2.1 (18.36, 28.63)	0.971

Table 4 Pain scores

	Placebo (n = 100) Mean ± SD (range)	EMLA 5% (n = 100) Mean ± SD (range)	Mean difference	*p*-value
Pain scores prior to ESWL (0 min)	1.1 ± 0.5 (0, 2)	0.9 ± 0.6 (0, 2)	0.2	$p = 0.011$
Pain scores at 15 min	5.4 ± 1.5 (0, 10)	4.1 ± 1.6 (2, 8)	1.3	$p < 0.001$
Pain scores at 30 min	6.0 ± 1.4 (1, 8)	3.8 ± 1.3 (1, 8)	2.2	$p < 0.001$
Pain scores at 45 min	4.6 ± 1.2 (1, 8)	3.1 ± 0.9 (0, 4)	1.5	$p < 0.001$

Table 5 Number of patients who received intravenous pethidine at each time point

	Placebo (n = 100)	5% EMLA (n = 100)	*p*-value
Pethidine at 15 minutes			< 0.001
- Yes	75	41	
- No	25	59	
Pethidine at 30 minutes			< 0.001
- Yes	80	19	
- No	20	81	
Pethidine at 45 minutes			< 0.001
- Yes	31	0	
- No	69	100	

Table 6 Patients with side effects of intravenous pethidine during lithotripsy

	Placebo (n = 100)	5% EMLA (n = 100)	*p*-value
No side effect	15	82	< 0.001
Nausea	40	6	< 0.001
Dizziness	67	8	< 0.001
Vomiting	3	4	0.700
Headache	28	6	< 0.001
Dyspnea	4	2	0.407

including nausea, dizziness and respiratory depression, which may require treatment or hospitalization[6-8]. Intravenous or intramuscular non-steroidal anti-inflammatory agents (NSAIDs) may be used, but these have been found to be inferior to opioids, and may also have gastrointestinal side effects or hypersensitivity effects. Regional and general anesthesia may also be employed during lithotripsy, but both require prolonged hospitalization, longer preparation time, carry their on considerable risk of complications, as well as being expensive.

Topical anesthetic agents have also been used for ESWL. A prospective, randomized, double-blind study found that 5% EMLA and intravenous fentanyl, compared with placebo and intravenous fentanyl, was not significantly more effective[9]. However, a study compared the analgesic effects of NSAIDs, intravenous opioids, intramuscular opioids and 5% EMLA at the time of lithotripsy and found no significant difference in VAS scores among the treatments[10]. Newer studies have found that the use of 5% EMLA makes patients more tolerant of ESWL, resulting in more successful outcomes[11,12]. Thus, 5% EMLA seems to be an interesting candidate for replacing or at least reducing the use of other established analgesics during ESWL. In the present study, intravenous pethidine was used as the main analgesic agent because of its effectiveness, low cost, and fewer side effects than other opioids.

In the present study, patients' baseline data were not significantly different between the two study groups. The number of shock waves and the amount of time spent during lithotripsy were controlled to make sure that they were the same for all patients. Important differences between the present and previous studies

included keeping the site of ESWL constant for all patients, who had either renal or upper ureteric stones, and the comparison of pethidine use and pethidine-related side effects between treatment groups. The application of EMLA was thus very precise and accurate, at the actual point of ESWL. While previous studies have used varying amounts of 5% EMLA, for example as much as 30 gm on an area as large as 300 cm^2 (15 × 20 cm^2), and with application times from60 to 90 minutes13,14, in the present study we were able to reduce the amount of 5% EMLA to only 2 gm on an area of only 10 cm^2, with an application time of 60 minutes.

The apparent significant reduction of pain and use of intravenous opioids in the 5% EMLA group in the present study seemed to suggest the possibility of using local analgesics as part of a pain management protocol in future patients with ureteric and renal calculi requiring ESWL.

Conclusions

The results of the present study showed that5% EMLA cream may be effectively used as a topical analgesia to help reduce intravenous opioid (pethidine) analgesia in patients undergoing renal or upper ureteric ESWL. Side effects of intravenous opioids and hospitalization time were significantly reduced as well.

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บทคัดย่อ

EMLA 5% สามารถใช้ทดแทนยาแก้ปวดแบบฉีดเข้าหลอดเลือดดำ Opioid (Pethidine) ขณะทำการสลายนิ่ว (ESWL) ในผู้ป่วยที่มีนิ่วบริเวณไต ท่อไตส่วนบนได้หรือไม่

สุรพงษ์ ธนวงศ์วิบูลย์, พบ., วว. ศัลยศาสตร์ทั่วไป, วว. ศัลยศาสตร์ระบบทางเดินปัสสาวะ
หน่วยศัลยศาสตร์ระบบทางเดินปัสสาวะ กลุ่มงานศัลยศาสตร์ โรงพยาบาลเลิดสิน กรมการแพทย์

ที่มาและความสำคัญ: มีคนไข้จำนวนมากที่มีข้อบ่งชี้ในการรักษานิ่วที่ไต, ท่อไตส่วนบน ด้วยวิธีการสลายนิ่ว (ESWL) การให้ยาระงับอาการปวดขณะทำสลายนิ่วที่นิยมใช้มากที่สุดคือการใช้ยากลุ่ม opioids ซึ่งได้ผลระงับอาการปวดดีเป็นที่น่าพอใจ แต่ผลข้างเคียงของยาแก้ปวดกลุ่มนี้ค่อนข้างมาก

วัตถุประสงค์: การศึกษานี้เป็นการศึกษาว่า EMLA 5% cream สามารถนำมาใช้ระงับอาการปวดขณะทำสลาย นิ่วได้ดีพอที่จะสามารถทดแทนการใช้ยากลุ่ม opioids เดิมได้หรือไม่ หรือสามารถลดปริมาณการใช้ยาและผลข้างเคียงของยาแก้ปวดกลุ่ม opioids ได้หรือไม่

วัสดุและวิธีการ: เป็นการศึกษาแบบ prospective, controlled, randomized, double-blind study โดยการสุ่มเลือกผู้ป่วยเป็น 2 กลุ่ม (A, B) กลุ่มละ 100 คน กลุ่ม A ทายา EMLA 5% cream กลุ่ม B ทายาหลอก (placebo) เปรียบเทียบ demographic data เพศ, อายุ, BMI, ตำแหน่ง และขนาดของนิ่ว, ASA class,โรคประจำตัวของผู้ป่วยทั้งสองกลุ่ม โดยควบคุมให้ตำแหน่งหรือจุดในการปล่อยคลื่นเสียง, เวลาและจำนวนนัดในการสลายนิ่วไม่แตกต่างกัน ใช้ NRS (numerical rating scale) เป็นตัวประเมินระดับความปวด (pain score)

ผลการศึกษา: ผลของการศึกษาพบว่ากลุ่มตัวอย่างทั้ง 2 กลุ่ม demographic data ไม่มีความแตกต่างกัน Pain score ในกลุ่มที่ได้รับการทายา EMLA 5% พบว่าน้อยกว่ากลุ่ม control ในขณะทำสลายนิ่วอย่างมีนัยสำคัญ ปริมาณยา opioids (pethidine)ในกลุ่ม control มีการใช้มากกว่าอย่างมีนัยสำคัญ จำนวนชั่วโมงที่อยู่โรงพยาบาลหลังการสลายนิ่วในกลุ่ม control มากกว่าอย่างมีนัยสำคัญ และผลข้างเคียงของยา IV opioids (pethidine) โดยกลุ่ม control พบว่า nausea, dizziness, headache มีจำนวนมากกว่าอย่างมีนัยสำคัญ

สรุป: EMLA 5% cream สามารถนำมาใช้ทดแทนยาแก้ปวดกลุ่ม opioids (pethidine) ในการระงับอาการปวดจากการสลายนิ่วที่บริเวณไต, ท่อไตส่วนบนได้ และสามารถช่วยลดปริมาณการใช้ยา opioids (pethidine) ส่งผลให้อาการข้างเคียงจากยาขณะหรือหลังทำสลายนิ่วลดน้อยลง คนไข้ไม่ต้องอยู่โรงพยาบาลนานเพื่อสังเกตอาการหรือรักษาผลข้างเคียงนั้น