Urol Res (2012) 40:575–579
DOI 10.1007/s00240-012-0468-0

ORIGINAL PAPER

Topical EMLA for pain control during extracorporeal shock wave lithotripsy: prospective, comparative, randomized, double-blind study

D. Gallego Vilar · G. García Fadrique · C. Di Capua Sacoto · J. Beltran Persiva · M. Perez Mestre · J. A. De Francia · I. Povo Martin · J. Miralles Aguado · C. Garau Perelló · L. Sanchis Verdu · J. Gallego Gomez

Received: 3 August 2011 / Accepted: 4 February 2012 / Published online: 4 May 2012

Abstract Patient collaboration in external shock wave lithotripsy (ESWL) is critical for its correct application, making proper analgesic selection indispensable. The aim of this study was to evaluate the efficacy of combined application of EMLA and intravenous (i.v.) pethidine compared with pethidine plus placebo cream in patients undergoing ESWL for ureteral and/or renal lithiasis. Prospective, controlled, randomized, double-blind study was conducted in patients receiving ESWL for renal and/or ureterolithiasis. The patients were randomly assigned to receive i.v. pethidine plus either EMLA cream (group A) or placebo hydrating cream (group B). Evaluated were type, location, and size of lithiasis, patient's sex, age, body mass index, comorbidity, Visual Analogue Scale (VAS) score of pain, and degree of lithiasis fragmentation. EMLA cream provided significantly better pain relief and lithiasis fragmentation and more completed ESWL treatment. Topical application of EMLA cream combined with i.v. pethidine improved VAS scores and lithiasis fragmentation and decreased the rate of withdrawal from ESWL procedure versus i.v. pethidine plus placebo therapy.

Keywords Lithotripsy · Pain · Complications

D. G. Vilar (✉) · I. P. Martin · J. M. Aguado · C. G. Perelló · L. S. Verdu · J. G. Gomez
Hospital General de Castellón, Castellon de la plana, Castellón, Spain
e-mail: dagalvi@hotmail.com

G. G. Fadrique
Hospital de Manises, Manises, Valencia, Spain

C. D. C. Sacoto
Hospital de La Plana, Vilareal, Castellón, Spain

J. B. Persiva · M. P. Mestre · J. A. De Francia
Hospital Provincial, Castellon de la plana, Castellón, Spain

Introduction

Extracorporeal shock wave lithotripsy (ESWL) has become the gold standard for the treatment of numerous urinary tract lithiasis [1, 2]. Patient collaboration during the procedure is critical for its correct application, making proper analgesic selection indispensable.

Pain from ESWL has multifactorial origin and can be explained as follows [3]: parietal pain that is derived from the continuous impact of shock waves on cutaneous nociceptors; visceral pain resulting from increases of intrapelvic pressure and renal capsule distension [4].

The most commonly used analgesics during ESWL include opioids, sedatives, nonsteroidal anti-inflammatory drugs (NSAIDS), and anesthetic topical creams. It has been shown that opioids provide adequate analgesic control but incur marked risk of side effects. Good results have also been reported with the use of local anesthesia for ESWL [5]. "Eutectic mixture of local anesthetic" (EMLA) is a type of topical cream that includes lidocaine (2.5%) and prilocaine (2.5%). This cream has a skin-penetrating depth of 4 mm and onset time of 10–20 min, and provides pain relief for ≤60 min [5].

The aim of this study was to evaluate the efficacy of combined application of EMLA plus intravenous (i.v.) pethidine compared with i.v. pethidine plus placebo cream in patients receiving ESWL for ureteral and/or renal lithiasis.

Materials and methods

In this prospective, controlled, randomized, double-blind study, patients scheduled to undergo ESWL for renal and/or ureteral lithiasis were randomly assigned by informatics system to receive in addition to i.v. pethidine either EMLA

cream (AstraZeneca; 1 g contains 25 mg of lidocaine and 25 mg of prilocaine; group A) or placebo hydrating cream (group B).

EMLA or placebo cream was topically applied covering an area of 10 cm^2 over the surface where the lithotripter nipple was applied 60 min prior to ESWL. All patients also received i.v. infusion of pethidine (50 mg) combined with metoclopramide (10 mg).

ESWL was performed using a Dornier Lithotripter SII. Ten minutes after completion of ESWL, patients were asked to provide a score from 0 to 10 using the Visual Analogue Scale (VAS) of pain with 0, 5, and 10 representing absence of pain, moderate pain, and unbearable pain, respectively, to indicate the pain intensity that was experienced during the ESWL procedure.

Variables evaluated included the type of lithiasis (radiopaque or radiotranslucent), location (with renal including the pelvis, major, mid, or minor calyx and ureter including subpyelic, lumbar, and pelvic), extent of lithiasis, patient's sex, age, body mass index (<25 thin people; >30 obesity), comorbidity, VAS score, and degree of lithiasis fragmentation in both groups using pretreatment and posttreatment radiological findings ("Δ lithiasis" variable, difference between baseline and residual lithiasis size following ESWL).

To evaluate the differences between pain levels experienced by the two groups, we quantitatively analyzed the clinical results. Chi-square test was used to test for statistical differences between the two groups. Multivariate analysis was performed using logistic regression to test for correlations among increased pain, patient demographics, size, type, and location of lithiasis, and number of waves and total energy used during the ESWL procedure. ANOVA test was used to evaluate homogeneity of the two groups. SPSS V.17.0 program was used for all statistical analyses; data are presented as mean ± standard deviation.

Results

A total of 434 patients who underwent ESWL over a period of 17 months were included. Patients' demographics are presented in Table 1. Of the 434 patients, 165 and 269 were assigned to groups A and B, respectively. ANOVA analysis confirmed that the two groups comprised homogeneous patient populations ($p < 0.05$; 95% CI).

The locations of the lithiases are shown in Figs. 1 and 2. The number of waves and total energy that were applied, type of lithiasis, pre- and post-ESWL sizes, number of patients who received an incomplete treatment and VAS scores are shown in Table 2.

In group A, 135 of the 165 patients (82%) completed the treatment. Following ESWL, 111 (82.2%) of the 135 patients showed no residual lithiasis, 21 (15.5%) had residual fragments, and 2 (1.5%) showed no signs of calculi dissolution. In group B, 211 of the 269 patients (78%) completed the treatment. Following ESWL, 165 (78.2%) of the 211 patients showed no residual lithiasis, 41 (19.41%) had residual fragments, and 5 (2.3%) showed no signs of calculi dissolution.

The differences between groups were statistically significant ($p < 0.05$; 95% CI). In groups A and B, 12 and 31 patients, respectively, did not complete the treatment because of intolerable pain; these results are significantly different ($p < 0.05$; 95% CI). VAS score of patients in group A was significantly lower than that of those in group B ($p < 0.05$; 95% CI). Multivariate analysis revealed that severe pain was reported, and both higher energy and more waves were used for group B versus group A ($p < 0.05$; 95% CI). No differences were found depending on lithiasis location (Table 3). 28 patients with BMI <25 and 21 with

Table 1 Demographic's of patients

	Group A	Group B
n	165	269
Age (years)	47.2 SD 16.3	43.6 SD 17.1
Men (*n*)	98	189
Women (*n*)	67	80
BMI	24.2 ± 7.2	25.1 ± 5.8
Comorbidity (*n*)		
Hypertension	56	91
Diabetes mellitus	43	71
Dyslipidemia	64	88
Hypercholesterolemia	37	89
Thin people	28	29
Obesity	21	42

n number of patients; *BMI* body mass index <25 normal weight/thin people, >29.9 indicating obesity; *SD* standard deviation

ANOVA test: $p = 0.021$; 95% CI

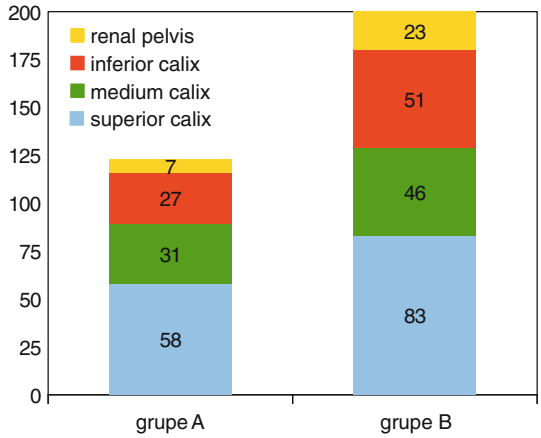

Fig. 1 Location of renal lithiasis by group. ANOVA test: $p = 0.132$; 95% CI

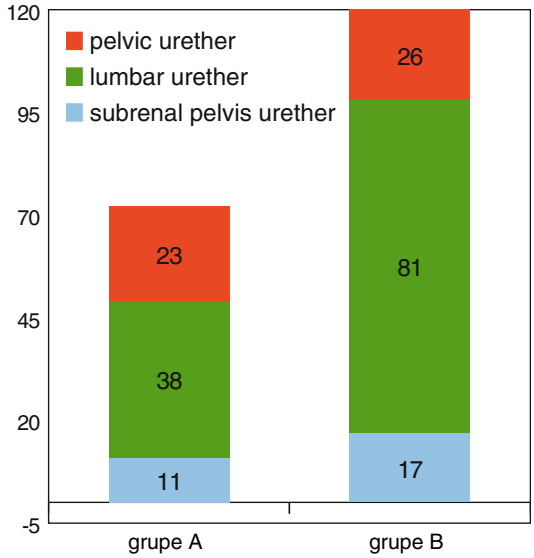

Fig. 2 Uretheral lithiasis location per groups. ANOVA test: $p = 0.071$; 95% CI

Table 2 Results of the treatment comparing group A (lidocaine and prilocaine) with group B (placebo)

	Group A	Group B
Radiotranslucent lithiases	27	43
Radiopaque lithiases	167	283
Pre-ESWL lithiasis size (mm)	33.23 SD 9.3	31.2 SD 18.6
Shock waves applied	1,982 SD 997	2,159 SD 1,112‡
Total energy applied	133.2 SD 46.7	141.1 SD 38.7†
Post-ESWL lithiasis size (mm)	16.1 SD 0.8	15.8 SD 0.64*
D lithiasis (mm)	17.13 SD 4.8	15.4 SD 5.4*
Incomplete treatment (*n*)	30	58*
Due to intolerable pain (*n*)	12	31*
Visual Analog Scale score	3.4 SD 1.6	4.1 SD 1.9*

n number of patients; *mm* millimeters; *SD* standard deviation

* $p < 0.005$ by Chi-square test; 95% CI

† Reg. Log; $p = 0.0094$, coefficient: 0.036; z score = 3.89

‡ Reg. Log; $p = 0.0067$, coefficient: 0.045; z score = 2.25

BMI >30 in group A, VAS in patients with BMI <25 versus >30 in group A was 3.4 versus 3.2 ($p > 0.05$) and VAS in patients with BMI <25 versus >30 was 4.3 versus 3.9 ($p > 0.05$), respectively, in group B (29 patients with BMI <25 and 42 patients with BMI >30), VAS differences between groups depending on BMI were not significantly different ($p > 0.05$; 95% CI).

Discussion

A number of medications and analgesic techniques have been used for the management of pain during ESWL. Opioids such as fentanyl, propofol, remifentanil, and sufentanil provide adequate analgesic control but incur marked risk of side effects including nausea and respiratory depression that require active patient monitoring and the presence of an anesthesiologist, thus increasing the resources needed for application of ESWL [6–8]. In this study, we opted to use pethidine i.v. infusion because it has fewer undesirable effects than other opioid substances. With respect to NSAIDS, studies of i.v. and intramuscular diclofenac reported weaker analgesic effects than i.v. opiates and secondary gastrointestinal and hypersensitivity effects [9–11]. Currently, the use of general anesthesia during ESWL is indicated only in selected cases [12], and local anesthesia can provide a favorable outcome [13–16]. However, both general and local anesthesia increase the duration and cost of the procedure.

Table 3 Pain in relation with the calculi location between group A (lidocaine and prilocaine) with group B (placebo)

	Group A	Group B
	N lithiasis/mean VAS	*N* lithiasis/mean VAS
Renal pelvis	7/3.6 SD 0.9	23/3.8 SD 1.0
Inferior calix	27/3.1 SD 1.1	51/4.6 SD 1.6
Medium calix	31/3.6 SD 1.1	48/4.1 SD 1.9
Superior calix	58/2.9 SD 0.8	83/4.5 SD 1.5
Pelvic urether	23/3.3 SD 1.6	26/3.8 SD 0.9
Lumbar urether	38/2.8 SD 1.8	81/4.0 SD 1.3
Subrenal urether	11/3.3 SD 0.9	17/3.7 SD 0.8

SD standard deviation

Log. Reg.; $p = 0.078$, coefficient: 0.15; z score = 1.14

In the past few years, the use of topical substances applied to the treatment site has increased. Some studies evaluated the efficacy of applying subcutaneous prilocaine 2 min prior to ESWL [17]. Prilocaine temporarily inhibits neuronal transmission and has a faster onset time and fewer associated side effects than lidocaine. Studies comparing its analgesic effect with that of intramuscular diclofenac showed better pain management with prilocaine [18]. In these papers, two different analgesic delivery methods (oral versus subcutaneous) were studied, but the placebo effect of prilocaine was not evaluated. However, the results of these studies are promising.

The efficacy of EMLA in combination with i.v. opiates has been studied previously. In a prospective, randomized, double-blind study, the effect of EMLA was evaluated in 83 patients who underwent ESWL, in which EMLA was applied in one group and placebo cream in another, with additional analgesia provided in the form of i.v. fentanyl in both groups [19]. In that study, no difference between the two groups was found in terms of pain management as determined by VAS [19]. In the present study, we chose to administer i.v. pethidine as a morphine adjuvant to achieve better pain tolerance with the same dose in both groups.

Only one previous study has compared the combined use of NSAIDs, i.v. opioids, intramuscular opioids, and EMLA for the management of pain during ESWL [20], and no significant difference was found in VAS scores. Thus, EMLA is considered adequate for the management of pain during ESWL.

In the present study, the patients who received EMLA had a mean VAS score of 3.4, which was significantly lower than that in those who received placebo cream (4.1).

Bárcena et al. [21] evaluated the use of EMLA in patients who could not tolerate a previous session of ESWL, and found that EMLA provided better pain tolerance and was associated with a higher degree of lithofragmentation. Yilmaz et al. [22] reported a higher degree of lithofragmentation in patients who received EMLA in conjunction with i.v. fentanyl compared with patients who only received i.v. fentanyl. However, neither of these studies evaluated the placebo effect of EMLA. We examined the placebo effect of topical EMLA by applying a similar amount of placebo cream to a control group of patients and measured lithofragmentation as the difference between the size of pre- and post-ESWL lithiases. We found a higher degree of lithofragmentation in patients who were treated with EMLA compared with those who received placebo cream (17.1 vs. 15.4 mm, respectively).

It is evident that more effective pain control during ESWL will lead to a lower incidence of incomplete treatments. In all, 7.3% of our patients who were treated with EMLA withdrew due to intolerable pain, whereas 11.5% of those who received placebo cream withdrew due to intolerable pain. Bárcena et al. [20] applied EMLA to the patients who previously could not tolerate ESWL due to pain and found that they could complete the repeat procedure. In two studies, in which the placebo effect of EMLA was specifically evaluated, no withdrawal occurred due to pain in the group of patients who were treated with EMLA [23, 24].

It is known that obesity is a problem to the successful treatment of renal stones. The ESWL table may not be able to support the weight of the patient, and the increased distance from the skin surface to the stone may render positioning of the stone at the focus of the shock wave impossible. There are studies in which [25] higher energy settings were implemented to achieve successful stone fragmentation in obese patients, but no higher flank pain was recorded. People with BMI <25 has lower distance from the skin surface to the target of the shock wave, this difference may lead to different pain status during ESWL comparing to obese patients. In our study, patients receiving EMLA cream with BMI <25 had higher VAS mean than >30 BMI patients (3.4 vs. 3.2), but no statistical significance was found. In group B, results were similar (mean VAS in patients with BMI <25 was 4.3 vs. 3.9 and in >30 BMI patients, no significantly different).

Multivariate analysis of our data revealed that the placebo group reported more severe pain and received both more total energy and a higher number of waves, unlike in a previous study [26]. On the other hand, Ganapathy et al. [19] found significantly decreased pain in patients who were treated with EMLA, and this effect was even more pronounced in those who received higher energy waves, consistently with our study.

Conclusions

Topical application of EMLA cream combined with i.v. pethidine decreased the rate of withdrawal from the ESWL procedure, and improved VAS scores and lithiasis fragmentation compared with i.v. pethidine plus placebo cream.

References

1. Chaussy C, Brendel W, Schmiedt E (1980) Extracorporeal induced destruction of kidney stones by shock waves. Lancet 13(2):1265–1268
2. Chaussy GC, Fuchs GJ (1989) Current status and future developments of non invasive treatment of urinary stones with extracorporeal shock waves lithotripsy. J Urol 141(3 Pt 2):782–789
3. Salinas AS, Lorenzo-Romero J, Segura M, Calero MR, Hernández-Millán I, Martínez-Martín M et al (1999) Factors determining analgesic and sedative drug requirement during extracorporeal shock wave lithotripsy. Urol Int 63:92–101
4. Weber A, Koehrmann KU, Denig N, Michel MS, Alken P (1998) What are the parameters for predictive selection of patients requiring anesthesia for extracorporeal shock wave lithotripsy? Eur Urol 34:85–92
5. Gupta NP, Kumar A (2008) Analgesia for pain control during extracorporeal shock wave lithotripsy: current status. Indian J Urol 24(2):155–158
6. Schelling G, Weber W, Mendl G, Braun H, Cullann H (1996) Patient controlled analgesia for shock wave lithotripsy: the effect of self administered alfentanil on pain intensity and drug requirement. J Urol 155:43–47
7. Gesztesi Z, Sa Rego M, White F (2000) The comparative effectiveness of fentanyl and its newer analogs during extracorporeal shock wave lithotripsy under monitored anesthesia care. Anesth Analg 90(3):567–570
8. Parkin J, Keeley FX, Timoney AG (2002) Analgesia for shock wave lithotripsy. J Urol 167(4):1613–1615
9. Husnu T, Serhan Y, Volkan H, Ozlem T, Bulent E, Bulent A et al (2010) Comparison of the Analgesic effects of dexketoprofen and diclofenac during shockwave lithotripsy: a randomized double-blind clinical trial. J Endourol 24(6):1031–1035
10. Yang CP, Cherng CH, Wong CS, Ho ST (2002) Effect of ketorolac and fentanyl combined with midazolam on analgesia and side effects during external shock wave lithotripsy. Acta Anaesthesiol Sin 40(1):9–12
11. Chia YY, Liu K (1998) Prospective and randomized trial of intravenous tenoxicam versus fentanyl and tramadol for analgesia in outpatient extracorporeal lithotripsy. Acta Anaesthesiol Sin 36(1):17–22

12. Ramakrishnan PA, Medhat M, Al-Bulushi YH, Nair P, Al-Kindy A (2007) Extracorporeal shockwave lithotripsy in infants. Can J Urol 14(5):3684–3691
13. Eaton MP, Chhibber AK, Green DR (1997) Subarachnoid sufentanil versus lidocaine spinal anesthesia for extracorporeal shock wave lithotripsy. Reg Anesth 22(6):515–520
14. Lau WC, Grenn CR, Faeber GJ, Tait AR, Golembiewski JA (1999) Determination of the effective therapeutic dose of intrathecal sufentanil for extracorporeal shock wave lithotripsy. Anesth Analg 89(4):889–892
15. Kanazi GE, Tran SB, Rizk L, Baraka A (2003) Multimodal spinal anesthesia. Middle East J Anesthesiol 17(2):265–273
16. Lau WC, Green CR, Faeber GJ, Tait AR Golembiewski JA (1997) Intrathecal sufentanil for extracorporeal shock wave lithotripsy provides earlier discharge of the outpatient than intrathecal lidocaine. Anesth Analg (6):1227–1231
17. Yilmaz E, Batislam E, Basar M, Tuglu D, Yuvanc E (2006) Can prilocaine infiltration alone be the most minimally invasive approach in terms os anesthesia during extracorporeal shock wave lithotripsy? Urology 68(1):24–27
18. Yilmaz E, Batislam E, Tuglu D, Yuvanc E (2008) Local anesthesia with 20-ml prilocaine infiltration: the ultimate point for analgesia during external shock wave lithotripsy? J Endourol 22(5):883–887
19. Ganapathy S, Razoi H, Moote C, Parkin J, Yee I, Gverzdys S et al (1996) Eutectic mixture of local anesthetics is not effective for extracorporeal shock wave lithotripsy. Can J Anesth 43(10):1030–1034
20. Basar H, Yilmaz E, Ozcan S, Buyukkocak U, Sari F, Apan A, Batislam E (2003) Four analgesic techniques for shockwave lithotripsy: eutectic mixture local anesthetic is a good alternative. J Endourol 17(1):3–6
21. Bárcena M, Rodríguez J, Gude F, Vidal MI, Fernández S (1996) EMLA cream for renal extracorporeal shock wave lithotripsy in ambulatory patients. Eur J Anaesthesiol 13(4):373–376
22. Yilmaz E, Batislam E, Basar MM, Tuglu D, Ozcan S, Basar H (2005) Effectiveness of eutectic mixture of local anesthetic cream and occlusive dressing with low dosage of fentanyl for pain control during shockwave lithotripsy. J Endourol 19(5):589–594
23. Tritrakarn T, Lertakyamanee J, Koompong P, Soontrapa S, Somprakit P, Tantiwong A, Jittapapai S (2000) Both EMLA and placebo cream reduced pain during extracorporeal piezoelectric shock wave lithotripsy with the Piezolith 2300. Anesthesiol 92(4):1049–1054
24. Monk TG, Ding Y, White PF, Albala DM, Clayman RV (1994) Effect of topical eutectic mixture of local anesthetics on pain response and analgesic requirement during lithotripsy procedures. Anesth Analg 79(3):506–511
25. Thomas R, Cass AS (1993) Extracorporeal shock wave lithotripsy in morbidly obese patients. J Urol 150:30–32
26. Eryldirim B, Kuyumcuoglu U, Tarhan F, Faydaci G, Uruç F (2009) Comparison of three analgesic treatment protocols for pain management during extracorporeal shock wave lithotripsy. Urol Int 82(3):276–279