

THE EFFICACY OF PIROXICAM/LIDOCAINE/CYCLOBENZAPRINE HYDROCHLORIDE TOPICAL GEL IN THE PAIN MANAGEMENT DURING EXTRACORPOREAL SHOCK WAVE LITHOTRIPSY (ESWL)

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Abstract

The aim of the study was to evaluate the efficacy of the combination for cutaneous application of piroxicam/lidocaine/cyclobenzaprine hydrochloride for the pain management during Extracorporeal Shock Wave Lithotripsy (ESWL). A number of 256 patients with renal and ureteral stones were randomly assigned to one of the 3 groups: group A (topical analgesic 30 minutes prior to ESWL), group B (topical analgesic 60 minutes prior to ESWL) and group C (no treatment prior the ESWL). The pain before and during the procedure was evaluated with a Visual Analogue Scale (VAS) and for each patient the rescue analgesic medication was quantified. Regarding age, weight, stone size, number of shock wave delivered and maximum voltage used, no statistical differences were noticed in the three groups ($p > 0.05$). The topical application of a gel with this analgetic combination before the ESWL provided significant relief of the pain during this procedure in comparison with no treatment. The topical analgesic before lithotripsy also reduced the need of rescue medication. The gel with piroxicam/lidocaine/cyclobenzaprine hydrochloride is a valuable alternative for the management of pain during ESWL.

Rezumat

Scopul studiului a fost de a evalua eficiența aplicării cutanate a unui gel cu piroxicam/lidocaină/clorhidrat de ciclobenzaprină în managementul durerii din timpul litotriției extracorporale cu unde de șoc (ESWL). Un număr de 256 de pacienți cu litiază renală și ureterală, randomizați, au fost grupați în 3 loturi, în funcție de terapia administrată înainte de efectuarea ESWL: grupul A (analgezic local cu 30 de minute înainte de ESWL), grupul B (analgezic local cu 60 de minute înainte de ESWL) și grupul C (fără tratament înainte de ESWL). Intensitatea durerii înainte și în timpul procedurii a fost evaluată prin *Visual Analogue Scale* (VAS), iar pentru fiecare bolnav a fost cuantificată medicația analgezică de urgență administrată. La cele 3 loturi nu a existat nicio diferență statistică privind vârsta, greutatea, dimensiunea calcului, numărul de unde de șoc efectuate sau voltajul maxim folosit ($p > 0,05$). Comparativ cu grupul fără tratament, în celelalte loturi, la care s-a aplicat local gelul analgezic înainte de ESWL, s-a observat ameliorarea durerii din timpul procedurii. De asemenea, această terapie administrată înainte de litotriție a redus și necesitatea medicației de urgență. Gelul cu piroxicam/lidocaină/clorhidrat de ciclobenzaprină reprezintă o alternativă valoroasă în managementul adecvat al durerii din timpul ESWL.

Keywords: ESWL, pain, topical gel, urolithiasis

Introduction

Extracorporeal Shock Wave Lithotripsy (ESWL), a non-invasive technique, is often used in urolithiasis treatment [1, 2, 3]. Although the newer generations

of lithotripters evolve and confer better compliance to the therapy, some of the patients do not tolerate the pain during the procedure and require intervention with analgesic agents during the procedure [1, 2].

The principle of ESWL is based on the renal stone disintegration by the focalized shock waves generated outside the body that pass through the skin, subcutaneous tissue, muscular wall, perirenal fat, renal parenchymal and basinet and discharge the energy at the urine/stone interface [2-5]. The procedure is painful with different degrees of pain perceived by the patients [2-5]. The analgesic arsenal for pain management in ESWL is vast and includes, in time, general anaesthesia, spinal anaesthesia, anaesthetic subcutaneous infiltration, oral and parenteral administration of opioids and nonsteroidal anti-inflammatory drugs (NSAIDs) and cutaneous analgesics and anaesthetics [2-5].

Therefore, the aim is to increase patients comfort but also to decrease the cost per procedure and reduce the pharmacological stress and toxicity. Furthermore, intricate and high risk techniques – as general and spinal anaesthesia – are avoided. Knowing the different needs for analgesia of the patients (which varies with the individual susceptibility to painful stimuli, the number and the intensity of the applied shocks), usually, they do not receive analgesic treatment before the ESWL, but have the possibility in any moment of the procedure to ask for rescue medication (patient-controlled analgesia). The preferred medication in such situations is parenteral analgesics due to their short latency of the onset. Unfortunately, the compliance to the parenteral medication is low. This encourages the studies focused on the possibility to reduce or replace parenteral analgesia [6, 7]. An option used in general surgery and also used in ESWL, especially for children, is ketamine which can provide “complete” anaesthesia combined with sedation, amnesia and pain relief, with the price of hallucinations, nightmares and possible tendency to depress airways reflexes [8, 9]. Cutaneous analgesia is a practical option. Recent clinical findings are promising – cutaneous analgesics application proved their efficacy in pain alleviation during ESWL [10-13].

Most of the clinical researches focused on the management of pain relief during ESWL studied the efficiency of topical NSAID, topical anaesthetic and also oral NSAIDs concomitant with a topical anaesthetic [10]; the use of a single product which combines both of the actives constitutes represents an element of novelty. The product investigated for the effect on pain during ESWL contains 3 active ingredients: piroxicam (a nonsteroidal anti-inflammatory drug), lidocaine (a topical anaesthetic) and cyclobenzaprine hydrochloride (a tricyclic analgesic).

The aim of the present study was to evaluate the efficacy of this topical combination piroxicam/lidocaine/cyclobenzaprine hydrochloride in the

alleviation of pain and the impact on the degree of rescue medication requirement during the ESWL.

Materials and Methods

This is a prospective and randomized research study conducted in our institute, after the approval of the protocol by the Ethics Committee. A number of 256 subjects, with confirmed renal stone to whom ESWL was recommended, were enrolled in the study. In addition, the informed consent was obtained for each included patient.

The inclusion criteria were adult patients with renal or ureteral stones, unilaterally or bilaterally localized, with stones smaller than 20 mm, eligible for ESWL, without known hypersensitivity to piroxicam, cyclobenzaprine, lidocaine or any other ingredient of the product and no previous exposure of ESWL. Exclusion criteria for this study were: stones larger than 20 mm, known hypersensitivity to any of the ingredients, asthma, nasal polyposis angioedema or rash induced by acetylsalicylic acid or other non-steroidal drug, pregnancy, bleeding disorders, active urinary tract infection, age under 18 years old. The patients were advised to stop using anticoagulant products 10 days, and any NSAIDs treatment 2 days before the ESWL procedure.

Prior to the ESWL procedure, the data recorded for each of the patient included age, gender, weight, height, the size and stone localization. Enrolled individuals were thoroughly evaluated regarding their clinical examination, family history, baseline biological and haematological tests, urine microscopy with culture and sensitivity. An intravenous urogram (IVU) was done in all the cases to assess the anatomical and functional aspects of the urinary system along with stone characteristics like stone size and position.

A second-generation electrohydraulic lithotripter with unique radiologic locating was used. The equipment outputs 1 shock/second. Usually, the treatment, extents up to 4000 shocks for ureteral stones and 3000 shocks for renal stones in sessions of 300 shocks. Initially low intensity shocks were applied 17.5 kV, which gradually increase up to 19 kV.

The patients were randomly assigned to one of the 3 groups: group A (topical analgesia with the gel containing piroxicam 0.5%, lidocaine 2%, cyclobenzaprine hydrochloride 0.5%, 30 minutes prior to ESWL), group B (topical analgesia with the same gel, 60 minutes prior to ESWL) and group C (no treatment prior the ESWL). For the patients in group A and B, 1 g of gel was spread and rubbed gently into the skin at the site of ESWL application, till complete absorption.

Each patient scored the pain before the procedure using a VAS (Visual Analogue Scale 0-10; 0 meaning *no pain* and 10 *immobilizing pain*) [14].

Each individual was catheterized before the procedure in order to be easily approached in case of analgesia requirement. When necessary, the patient received rescue medication – 100 mg of tramadol. After the ESWL, each subject was asked to score the pain perceived during the procedure. Additionally, the rescue medication, number and intensity of shocks and procedure duration were quantified for each of them.

Statistical analysis

ANOVA test was used to compare demographic data and Z-test to compare the pain score between the

three groups. A p value less than 0.05 was considered to be statistically significant.

Results and Discussion

The demographic data, stone localization and size, maximum energy, number of shock waves and procedure duration are represented in Table I. The characteristics of the groups were similar with no statistically significant difference between the groups.

Table I

Demographic data, stone size, stone localization and ESWL procedure parameters

Data	Group A	Group B	Group C	p	
Number of patients	90	85	81		
Female/Male Ratio	42 : 39	60 : 30	46 : 39	0.10	
Age	47.21 ± 15.01	49.53 ± 12.24	48.04 ± 13.51	0.51	
BMI	26.83 ± 5.73	27.56 ± 3.86	26.86 ± 4.00	0.51	
Localization of stone*	CCM	11 (12.22%)	8 (9.41%)	6 (7.41%)	
	CCS	4 (4.44%)	2 (2.35%)	9 (11.11%)	
	CCI	21 (23.33%)	16 (18.82%)	15 (18.52%)	
	CUL	20 (22.22%)	17 (20.00%)	16 (19.75%)	
	CUP	10 (11.11%)	12 (14.12%)	14 (17.28%)	
	CB	24 (26.67%)	27 (31.76%)	20 (24.9%)	
	STST	-	3 (3.53%)	1 (1.23%)	
Number of stones larger than 3 mm**	1.36 ± 0.80	1.11 ± 0.48	1.21 ± 0.49	0.10	
Stone size (mm)	8.91 ± 3.38	8.92 ± 3.59	8.03 ± 2.79	0.14	
Shock wave	2272.41 ± 841.88	2219.28 ± 796.40	2216.88 ± 938.84	0.11	
Shock waves maximum energy (kV)	19 ± 0.00	19 ± 0.00	19 ± 0.00	1.00	

* CCM = middle calyx, CCS = upper calyx, CCI = lower calyx, CUL = ureteral lumbar, CUP = ureteral pelvic, CB = pyelic, STST = Steinstrasse.

** in case that a patient presented more than one calculus larger than 0.3, only the largest calculus was considered.

The VAS score for the pain perceived before and during the ESWL and the level of tramadol consumption are represented in Table II. Mean VAS score during ESWL in group A was 3.76 ± 1.03, in group B 3.40 ± 0.83 and in group C 5.38 ±

1.46, respectively. The VAS score in group A and group B was significantly lower than in group C (control) – Z-test + 6.20, p < 0.0001, Z-test + 8.59, p < 0.0001, respectively.

Table II

Data for pain VAS score, rescue medication, adverse reactions

	Group A	Group B	Group C	p
VAS score before ESWL	0.43 ± 1.04	0.53 ± 0.83	0.60 ± 0.93	0.49
VAS score during ESWL (p value*)	3.76 ± 1.03 p < 0.0001*	3.40 ± 0.83 p < 0.0001*	5.38 ± 1.46	
Difference between VAS score during and before ESWL (p value*)	3.32 ± 1.47 p < 0.0001*	2.87 ± 1.24 p < 0.0001*	4.78 ± 1.59	
Rescue medication ODD Ratio**	7 (7.78 %) 0.57	4 (4.70 %) 0.34	11 (13.58 %)	

* p value for the statistical significance between active and control group

** relative risk for appealing at rescue medication in group A and B versus group C

Topical application of a gel with the combination piroxicam/lidocaine/cyclobenzaprine hydrochloride before the ESWL was linked with significantly lower values for VAS score of the pain during ESWL. These results suggested that topical analgesic treatment before ESWL provides significant relief of the pain during ESWL procedure in comparison with no treatment. A

statistically significant differences was noticed also between the groups A and B – Z-test = 2.20, p < 0.05. Although both of the therapy schemes, 30 or 60 minutes before lithotripsy, were effective in pain alleviation, the use of the gel 60 minutes before procedure was significantly more efficient.

The topical analgesic gel before lithotripsy also reduced the usage of rescue medication. If in group

C 11 patients (13.58%) asked for rescue medication, in group A and B, only 7 (7.78%), respectively 4 (4.7%) subjects required rescue medication. A significantly lower risk for the need of rescue medication was observed in group A and B in comparison with group C – OR = 0.54 and 0.34, respectively. By assessing all data, only 11 men (10.02% of men) and 11 women (7.43%) asked for rescue medication. No side effect and

local skin reaction were reported in the groups that received topical medication.

The Pearson correlation coefficient for body mass index (BMI), size stone, number of shocks and VAS score during lithotripsy was calculated (Table III). No significant correlation between BMI, size stone and number of shocks with VAS score was detected in group B and C. A significant correlation between BMI and stone size with VAS was highlighted for the patients in group A.

Table III
Correlation matrix in group A, B and C

Correlation in group A	Pearson correlation	p value
Age and VAS score	-0.17	0.10
BMI and VAS score	-0.14	0.19
Stones size and VAS score	0.05	0.65
Number of shocks and VAS score	0.14	0.21
Correlation in group B	Pearson correlation	p value
Age and VAS score	-0.09	0.40
BMI and VAS score	-0.21	0.06
Stones size and VAS score	0.01	0.95
Number of shocks and VAS score	0.12	0.26
Correlation in group C	Pearson correlation	p value
Age and VAS score	-0.11	0.35
BMI and VAS score	-0.17	0.13
Stones size and VAS score	0.02	0.89
Number of shocks and VAS score	-0.05	0.65

ESWL represents the first treatment option of renal stone between 5 - 20 mm, applied in 90% of cases [15]. With the first generation of lithotripters that were developed in the 80's, the procedure was performed under general or spinal anaesthesia, because it was extremely painful [16]. The technique evolved and nowadays, optimized devices, with new types of shock wave generators, improved ESWL procedure that is better tolerated and can be performed under analgesia, rather than anaesthesia [17].

Although the procedure remains painful, in most of the cases the patient tolerates the pain without the use of any analgesic intervention. In current practice, the patients receive no analgesic treatment before intervention, but have the possibility to ask for rescue medication (parenteral opioids) in case of unbearable pain during ESWL. The opioids have the disadvantage of presenting a large scale of side effects like respiratory depression, nausea and vomiting [18, 19]. Among the opioids, tramadol hydrochloride is one of the most used analgesics in rescue medication for ESWL [17, 19]. In usual therapeutic doses, no clinically significant respiratory depression, occur [17, 20]. However, parenteral doses of 100 mg of tramadol used during ESWL are linked with high rates of nausea and vomiting (25%) [17, 21, 22]. Therefore, further clinical and experimental trails are required to

investigate the possibilities to limit even more the use of analgesics like tramadol.

Topical anaesthetic application (especially lidocaine/prilocaine) before the procedure was also reported in different studies [12, 13, 23-25]. It was used alone or in combination with analgesics (NSAIDs or opioids) and it was found to be safe and effective in some of the studies [12, 13, 23-25].

Kumar *et al.* determined in a study of 240 patients undergoing ESWL that the use of a topical anesthetic EMLA (lidocaine 2.5%/prilocaine 2.5%) before the procedure, together with orally administered diclofenac, prevented the need of parenteral analgesics [13]. Basar, included in a trial 160 patients undergoing ESWL, determined that local EMLA (lidocaine 2.5%, prilocaine 2.5%) led to a decrease of intravenous analgesic (fentanyl), confirming the results of a previous research, performed by Xavier [10, 26]. NSAIDs agents (*e.g.*: diclofenac, ketorolac and piroxicam) can also be used for pain relief during ESWL procedure [17]. Previously, they were used intravenously, intramuscularly, orally or rectally, but studies for the effect of topical NSAIDs were also performed, with good results. Iqbal, in a study performed on 50 patients determined that diclofenac is safe for analgesia during ESWL, and diclofenac gel together with diclofenac intramuscular administration presented a better pain relief control compared to diclofenac gel alone [27]. Moazeni-Bistgani *et al.* emphasized

in a study with 159 patients diagnosed with urolithiasis undergoing ESWL that both lidocaine gel and piroxicam gel administered 30 minutes before the procedure, efficiently improved pain perception by the patients and the necessity of intravenous analgesia [13, 25, 28]. Considering these findings, cutaneous diclofenac and piroxicam seem to find their place in the treatment plan for the patients undergoing ESWL [13, 25, 28].

The present research was focused on the investigation of the possibility to increase the comfort of the patients undergoing ESWL, by mitigating the pain and, as well, reducing the use of rescue medication, when applying a cutaneous gel containing the combination of an NSAID, a topical anaesthetic and a tricyclic analgesic before the procedure. From our knowledge, this is the first study focused on the effects of a topical product containing a combination of NSAID, local anaesthetic and tricyclic painkiller used in the pain management during ESWL. Our results are in accordance with previous researches that concluded that topical anaesthetic and topical NSAIDs represent a useful option for pain management during ESWL.

In addition, the current study determined that the timing for topical application is very important, as superior results were obtained in the case of 60 minutes than 30 minutes administration before ESWL. The timing of topical agent application is essential for both pain reduction and rescue medication consumption. The patients in the group that received the gel 60 minutes before the procedure presented lower pain score and seldom asked for rescue medication. It seems that the 60 minutes application prior to the procedure provides a more close to maximum effect of this gel. As in many studies topical agents, especially topical NSAIDs [17, 27], were applied 30 minutes before the procedure, we consider that further studies are necessary to investigate the best moment for topical analgesics administration.

Furthermore, mean pain scores during the ESWL procedure were not affected by stone size and number of shocks in neither of the groups. In all groups, a tendency of higher VAS score was noticed in younger patients with a lower body mass index, but the correlation factors were under the level of statistical significance ($p > 0.05$). Similarly, the lack of association between pain perception and patients' characteristics was found in other researches [17, 29, 30]. In accordance with the results of other previous researches, we also found a better tolerability of the pain in women than in men, in all three group [30]; in contrast, Demir and Madbouly found no correlation of pain during ESWL and gender [11, 29].

Conclusions

The use of the combination piroxicam 0.5%, lidocaine 2% and cyclobenzaprine hydrochloride 0.5% in a single cutaneous preparation offers a better compliance of the patient to the treatment than the standard protocol, which does not use any analgesic medication before the ESWL procedure. Although the use of the gel 30 minutes before the procedure was found effective, but the 60 minutes application before the procedure significantly reduced the pain perception and the level of opioid consumption.

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