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Comparison of the analgesic effects of multimodal approach and fentanyl alone during shock wave lithotripsy

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Background : *So far, there has been no consensus on pain control during extracorporeal shock wave lithotripsy (ESWL).*

Objective : *To compare the analgesic effects of etoricoxib plus fentanyl with placebo plus fentanyl during ESWL in a prospective, randomized clinical trial.*

Methods : *Ninety-four patients were randomized into two groups: group A (n = 48) received etoricoxib 90 mg orally 1 hour and fentanyl 50 μg intravenously 15 minutes before procedure; group B (n = 46), placebo drug were given orally 1 hour and fentanyl 50 μg intravenously 15 minutes before procedure. Pain assessment was done with the 10-score linear visual analogue pain scale (VAS) before procedure (0 minute) and then every 15 minutes (15, 30 and 45 minutes) until the procedure was finished. The adverse effects were recorded immediately postoperative periods and at 24-hr postoperative periods.*

Results : *Mean difference of VAS between group A and B at 0, 15, 30 and 45 minutes were -0.14 (P = 0.530), 0.36 (P = 0.453), -0.15 (P = 0.793) and -0.12 (P = 0.822), respectively. The differences were not statistically significant. In group A, one patient (2%) had urticaria and another (2%) had petechiae at immediate post-operative, and another (2%) at 24-hr postoperative periods.*

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Conclusion : *Our study shows that the analgesic efficacy of multimodal approach by etoricoxib and fentanyl is insignificantly different from that of placebo and fentanyl.*

Keywords : *ESWL, analgesic, etoricoxib, fentanyl.*

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นนท์ ว่องวิทวัส. การศึกษาเปรียบเทียบระหว่างการใช้ยาหลายกลุ่มเทียบกับยา fentanyl เพียงอย่างเดียวในการระงับปวดขณะสลายนิ่วด้วยคลื่นกระแทกจากภายนอก. จุฬาลงกรณ์เวชสาร 2560 ม.ค – ก.พ.; 61(1): 31 – 9

บทนำ : *ความปวดจากการสลายนิ่วด้วยคลื่นกระแทก นอกจากจะมีผลต่อความสำเร็จของการสลายนิ่วแล้ว ในปัจจุบันยังไม่มีวิธีการระงับปวดจากการสลายนิ่วที่เป็นมาตรฐาน*

วัตถุประสงค์ : *เปรียบเทียบประสิทธิภาพของการระงับปวดวิธีใหม่ คือ ยาระงับปวดอีโทริคอกสิบ (Etoricoxib) ร่วมกับการให้ยาระงับปวด Fentanyl เปรียบเทียบกับการระงับปวดวิธีที่ใช้อยู่ปัจจุบัน คือ การใช้ยาระงับปวด Fentanyl อย่างเดียวในการระงับความปวดจากการสลายนิ่วด้วยคลื่นกระแทก*

วิธีการศึกษา : *ผู้ป่วยโรคนิ่วในทางเดินปัสสาวะที่ได้รับการรักษาด้วยวิธีการสลายนิ่วด้วยคลื่นกระแทก จำนวน 94 ราย ถูกแบ่งเป็น 2 กลุ่มโดยวิธีการสุ่ม กลุ่มทดลองได้รับยาอีโทริคอกสิบ 90 mg ร่วมกับยา Fentanyl 50 μg ก่อนการสลายนิ่ว กลุ่มควบคุมได้รับยา Fentanyl 50 μg ร่วมกับยาหลอกก่อนการสลายนิ่ว วัดความปวดจากการสลายนิ่วด้วยการให้คะแนนเป็นตัวเลข (visual analogue pain scale, VAS) คะแนนเริ่มตั้งแต่ 0 - 10 โดยวัดตั้งแต่ก่อนเริ่มสลายนิ่ว (0 นาที) และหลังจากนั้นทุก 15 นาที (15, 30 และ 45 นาที) และบันทึกอาการไม่พึงประสงค์หลังสลายนิ่วทันที และ 24 ชั่วโมงหลังสลายนิ่ว*

ผลการศึกษา : *ผลต่างของค่าคะแนนความปวดระหว่างสองกลุ่มที่เวลา 0, 15, 30 และ 45 นาที เท่ากับ -0.14 (P = 0.530), 0.36 (P = 0.453), -0.15 (P = 0.793) และ -0.12 (P = 0.822) ซึ่งไม่พบแตกต่างอย่างมีนัยสำคัญทางสถิติ สำหรับอาการไม่พึงประสงค์ในกลุ่มทดลอง พบว่ามีผื่นคัน 1 ราย และจ้ำเลือด 1 รายหลังสลายนิ่วทันทีและพบมีจ้ำเลือด 1 รายที่ 24 ชั่วโมงหลังสลายนิ่ว*

สรุป : *การให้ยาอีโทริคอกสิบ ร่วมกับการให้ยาระงับปวด Fentanyl ไม่ทำให้ความปวดจากการสลายนิ่วลดลงเมื่อเทียบกับการให้ยา Fentanyl อย่างเดียว*

คำสำคัญ : *การระงับปวด, การสลายนิ่วด้วยคลื่นกระแทก, อีโทริคอกสิบ, fentanyl.*

Extracorporeal shock wave lithotripsy (ESWL) is one of major treatment alternatives for urinary system stone disease management[1], as it has high efficacy and a low complication rate. Although non-invasive, it can cause significant pain and anxiety during the procedure.[2, 3] Pain during ESWL may lead to defocussing through voluntary and involuntary patient movement and can cause increased respiratory motion, both resulting in a reduced hit rate with a reduced stone fragmentation and a lower overall stone clearance. Various analgesics and anesthetic agents ESWL have been tried to decrease pain, still there is no a standard guidelines for the pain management. In clinical practice, the non-steroid anti-inflammatory drugs (NSAIDs) and opioids are the most widely used as pain therapy during ESWL procedure. The use of opioids is associated with potential complications such as respiratory depression, bradycardia, hypotension, nausea, vomiting and prolong recovery time. [4-10] NSAIDs is associated, however, with gastrointestinal disturbances, hypersensitivity reaction and coagulation disorder.[11]

The aim of present prospective randomized study was to evaluate the efficacy of etoricoxib and fentanyl compared with placebo and fentanyl in patients undergoing ESWL.

Materials and Methods

This was a prospective randomized study conducted at Roi-Et Hospital from October 2016 to November 2016 after obtaining approval from the ethics committee of the hospital and written consents from the patients. These patients were recruited from the outpatient clinic of the Department of Urology. The following inclusion criteria were: all patients with urolithiasis scheduled for ESWL at our hospital (renal stone size of less than 2 cm or ureteral stone size of less than 1 cm), aged more than 18 years old. Patients underwent a complete history and physical examination before ESWL. Exclusion criteria included allergy to the study medications, patients taking NSAIDs before treatment, having severe cardiovascular, pulmonary, liver and renal disease, bleeding disorder, peptic ulcer, active urinary tract infection, analgesic/narcotic dependency. Assessment of the stone size were established by intravenous urography. Pre-ESWL ureteral stents were placed when clinically indicated. Age, weight, height, body mass index (BMI), side, stone size, stone location, history of ESWL, ureteral stent insertion, number of shockwaves delivered, maximum energy level(kV) used for each patient were recorded.

Our sample size was determined to have less than a 10% confidence interval (CI) with 80% power. A sample size of 94 was estimated as a minimum of these criteria, and we sought to enroll 94 patients. The patients were randomized into two groups. The patients in group A (n = 48) received etoricoxib 90 mg orally 1 hour and fentanyl 50 μg intravenously 15 minutes before procedure; and, group B (n = 46), placebo were given orally 1 hour and fentanyl 50 μg intravenously 15 minutes before procedure. Procedure was conducted using Medispec Lithotripter E2000. Pain assessment was done with the 10-score linear visual analogue pain scale (VAS) before procedure (0 minute) and then every 15 minutes (15, 30 and 45 minute) until the procedure. The adverse effects were recorded immediately and at 24-hr post-operatively.

So for statistical analyses, STATA 13 (STATA Corp, College Station, TX,USA) was used. Independent *t* test was used to compare means of VAS score between the two groups if the outcomes were normally distributed. A probability level of $P < 0.05$ was consider significant.

Results

The patients' mean age, body mass index (BMI), side, stone size, stone location, history of ESWL, ureteral stent insertion, number of shockwaves delivered and maximum energy level (kV) used in each group were recorded and presented in Table 1. The characteristics of the patients in each group were similar. Mean VAS scores in group A at 0, 15, 30 and 45 minutes were 1.23 ± 1.10, 3.73 ± 2.15, 5.59 ± 2.68 and 6.43 ± 2.46, and group B at 0, 15, 30 and 45 minute were 1.09 ± 1.09, 4.09 ± 2.45, 5.44 ± 2.57 and 6.31 ± 2.18, respectively. After we tested that the data set was normally distributed, Independent *t* test was used to compare means of VAS score between the two groups. Mean difference of VAS between groups at 0, 15, 30 and 45 minute were -0.14 (P = 0.530), 0.36 (P = 0.453), -0.15 (P = 0.793) and -0.12 (P = 0.822), respectively thus the differences were not statistically significant (Table 2). There was no major complication such as subcapsular hematoma and none of the patients needed hospital stay after ESWL. In group A, one patient (2%) had urticaria, another (2%) had petechiae immediately and another (2%) had petechiae at 24-hr postoperatively. (Table 3).

Table 1. Demographic variables of study population.

Characteristics	Group A (n = 48)		Group B (n = 46)	
	Number	Percent	Number	Percent
Gender				
Male	14	(29.20)	17	(37.00)
Female	34	(70.80)	29	(63.00)
Age (years)				
Mean (± SD)	56.23	(± 10.21)	55.17	(± 10.85)
Median (min: max)	57.00	(27.0:78.0)	53.50	(34.0:80.0)
Education level				
Primary	33	(68.70)	39	(84.80)
Secondary	14	(29.20)	6	(13.00)
University	1	(2.10)	1	(2.20)
BMI (kg/m^2)				
Mean (± SD)	24.71	(± 4.38)	24.04	(± 4.26)
Median (min: max)	24.56	(15.40:33.90)	23.74	(14.90:35.80)
Stone location				
Kidney	41	(85.42)	39	(84.78)
Ureter	7	(15.48)	7	(15.22)

Table 1. (Con) Demographic variables of study population.

Characteristics	Group A (n = 48)		Group B (n = 46)	
	Number	Percent	Number	Percent
Side				
Left	23	(47.92)	19	(41.30)
Right	25	(52.08)	27	(58.70)
Stone size (cm)				
Mean (± SD)	1.04	(± 0.60)	1.06	(± 0.50)
Median (min: max)	0.95	(0.3:3.5)	1.00	(0.2:2.3)
History of ESWL				
Yes	29	(60.42)	25	(54.35)
No	19	(39.58)	21	(45.65)
Ureteral stent				
Yes	8	(16.67)	4	(8.70)
No	40	(83.33)	42	(91.30)
No. of shock wave				
Mean (± SD)	3581.25	(± 743.67)	3776.09	(± 547.39)
Median (min: max)	4000	(1500:4000)	40000	(1700:4000)
Energy level (kV)				
Mean (± SD)	22.34	(± 0.80)	22.23	(± 1.08)
Median (min: max)	22.50	(17.5:22.5)	22.5	(17.5:22.5)

Table 2. VAS and mean difference at 0, 15, 30 and 45 minute.

Outcomes	Group A (mean ± SD)	Group B (mean ± SD)	Mean difference	95% CI of Mean difference	*P*-value
1. Pain at 0 minute	1.23 ± 1.10	1.09 ± 1.09	-0.14	-0.59 to 0.31	0.530
2. Pain at 15 minutes	3.73 ± 2.15	4.09 ± 2.45	0.36	-0.59 to 1.30	0.453
3. Pain at 30 minutes	5.59 ± 2.68	5.44 ± 2.57	-0.15	-1.25 to 0.96	0.793
4. Pain at 45 minutes	6.43 ± 2.46	6.31 ± 2.18	-0.12	-1.14 to 0.90	0.822

Table 3. Complications observed in this study.

Complications	Immediately postoperatively				24-hr postoperatively			
	Group A (n = 48)		Group B (n = 46)		Group A (n = 48)		Group B (n = 46)	
	No.	%	No.	%	No.	%	No.	%
No	46	95.83	46	0	47	97.92	46	100
Echymosis	1	2.08	0	0	1	2.08	0	0
Urticaria	1	2.08	0	0	0	0	0	0

Discussion

Shock wave related pain is an important side effect of ESWL. Its pathogenesis has not yet been totally understood but cavitation seems to play a key role, rather than direct mechanical effects on nociceptive nerve endings. [12, 13] Several physical variables influencing treatment-related pain have been identified: the type of shockwave source, size and site of stone burden, peak pressure of shockwaves, diameter of the focal zone, and the size of the aperture of shockwave source reflecting the area of shockwave entering the skin.[14-16] Furthermore, responsible factors for pain perception during ESWL are: patient-related factors like age, gender, and body habitus.[17] As for maximal patient comfort, the most suitable drug for ESWL should provide adequate analgesia, sufficient sedation and minimal side effects and rapid recovery.

Various opioids (morphine, pethidine, tramadol, and fentanyl) have been given during ESWL. Among the various opioids, fentanyl is a strong narcotic. It has a rapid onset and a short duration of action. It provides an acceptable condition during ESWL, therefore, it is commonly used. However, if fentanyl is used, the respiration should be carefully monitored with continuous noninvasive pulse oximetry due to its marked respiratory depressive effect. [18]

NSAIDs have been extensively used in ESWL. By inhibiting the enzyme cyclooxygenase (COX), NSAIDs reduce the synthesis of prostaglandins, which act as messengers in inflammatory processes; they reduce the renal blood flow, the renin release and glomerular filtration rate. On the other hand, by blocking the synthesis of thromboxane, they also have an antithrombotic effect and affect hemostasis. Selective cyclooxygenase-2-inhibitor (COX-2), lacks the potential adverse events of a COX-1 inhibition, such as gastroduodenal ulceration and bleeding or impairment of platelet function[19, 20], is appropriate for ESWL-induced pain. They are not widely used for pain relief during ESWL, only parecoxib, which can be administered IV or IM, has recently been investigated, showing a limited analgesic effect which is less effective than fentanyl.[21] Rofecoxib is another COX-2 inhibitor, which shows good pain relief after ESWL, but it has been withdrawn from the market due to safety concerns. [22]

In our study, multimodal analgesics approach was used to avoid excessive dosing of one agent and the possibility of ensuing interaction

by administering a combination of opioid and COX-2 inhibitor. We showed the analgesic effects of multimodal approach; 90 mg of etoricoxib and 50 μg of fentanyl, as our standard agent for analgesia during ESWL which its efficacy is superior to and fentanyl alone. The VAS scores between two groups were not different. The rather limited analgesic effect in this study was probably due to the fact that the dose of fentanyl used in this study was already adequate , therefore, adding another medication did not relief any more pain. ESWL procedure causes only mild to moderate pain that it is not enough to show the effect of multimodal approach. As far as we know, this is the first study of multimodal analgesic approach (opioid and NSAIDs) to control pain during ESWL. Therefore further studies are needed to evaluate the efficacy of analgesic effect of multimodal analgesic approach.

Conclusion

Our study shows that the analgesic efficacy of multimodal approach by etoricoxib and fentanyl is not different from that of placebo and fentanyl.

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