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COMPARISON OF ANALGESIC EFFECT OF PREGABALIN-FENTANYL AND MIDAZOLAM-FENTANYL COMBINATIONS ON THE SEVERITY OF PAIN IN THE PATIENTS UNDERGOING EXTRACORPOREAL SHOCK WAVE LITHOTRIPSY: A DOUBLE-BLIND CLINICAL TRIAL

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ABSTRACT

Background and Objective: Kidney stone disease goes back to thousands of years ago. Extracorporeal Shock Wave Lithotripsy (ESWL) is currently the first line treatment for this disease. Different analgesics were already used to relieve pain in the patients but they still complain about their pain. Therefore, the effect of two combinations of pregabalin-fentanyl and midazolam-fentanyl was investigated in controlling pain in the patients undergoing ESWL in this study.

Materials and Methods: This was double-blind clinical trial on 141 patients visiting Lithotripsy Unit in Peymaniyeh Hospital in Jahrom Town.

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The participants were selected using a simple sampling method. Inclusion criterion was 8mm < kidney stone < 20mm. Exclusion criteria were 20 kg/m^2 < body mass index (BMI) < 30

kg/m^2, a history of mental disorders, namely addiction to analgesics and opiates. Finally, the patients were randomly assigned to two groups. One microgram per kilogram fentanyl was administered intravenously and 300mg pregabalin was given orally to the patients ten minutes before surgery in the first group (pregabalin-fentanyl and n = 47). One microgram per kilogram fentanyl and one microgram per kilogram midazolam were injected intravenously to the patients ten minutes prior to operation in the second group (fentanyl-midazolam and n = 46). Then, standard shock wave lithotripsy was carried out in both groups. The severity of pain was measured every 20 minutes during the operation and two hours after the operation using the Visual Analog Scale for Pain (VAS Pain). The collected data was analyzed using SPSS version 21. Descriptive statistics (mean, standard deviation and percent) and analytical statistical tests (Mann-Whitney and Chi-square) were used to analyze the data.

Results: The mean age of participants was 43.80±13.71 in the first group (pregabalin + fentanyl) and 39.0±11.19 in the second group (midazolam + fentanyl). Chi-square test results were matched in both groups in terms of age, gender, number of shocks and size of the stone. The Mann-Whitney test results showed a significant difference between the first and second groups in terms of pain score from the first 20 minutes up to 2 hours after drug administration (p-value<0.05). The results also showed that the number of patients experiencing higher than average severity of pain in the second group was significantly less than the first group (p-value<0.05).

Conclusion: The results of this study showed that the number of patients experiencing higher than average severity of pain in the group receiving midazolam-fentanyl combination was less than the group receiving pregabalin-fentanyl combination. Therefore, it can be deduced that fentanyl in combination with midazolam has a greater analgesic effect on pain relief in the patients undergoing ESWL.

Keywords: pregabalin-fentanyl, midazolam-fentanyl, pain, extracorporeal shockwave lithotripsy

INTRODUCTION

Kidney stone disease is one of the oldest diseases. Many people are dealing with this disease for thousands of years (1). Some substances deposit in the supersaturated urine and form stones (2). The prevalence of this disease varies from 4% to 15% worldwide (3). Extracorporeal Shock Wave Lithotripsy (ESWL) is currently the first line treatment for the patients with kidney stones. The patients undergoing ESWL still complain about their pain despite many efforts made to control and manage postoperative pain (4). Several physical

variables are already identified that affect the severity of pain in the patients undergoing ESWL including source of shockwave, size and location of the stone and pressure threshold for shock wave (7-5). Several patient-related factors were also identified that are effective in severity of pain including age, gender and physical characteristics (8). It was also shown that young female, depressed, anxious and thin patients have experienced more pain during the operation (10, 9). Different analgesics are needed to control the pain caused by shock waves in addition to invention of new generations of ESWL [for complete pain relief in the patients]. These analgesics include opioids (e.g. morphine and fentanyl), non-steroidal anti-inflammatory drugs (e.g. ketorolac, propofol and piroxicam) and cutaneous creams including eutectic mixture of local anesthetic cream (EMAA). These are either used alone or in combination with other drugs. Each of these has some advantages and disadvantages (11 and 12). Fentanyl is a potent industrial narcotic with the greatest efficacy in the shortest time. This drug acts as a strong μ-opioid receptor agonist and moderates the severity of pain in the patients undergoing ESWL. For this reason, it is commonly used to relieve pain (13). Such opioids as fentanyl can be used alone or in combination with other analgesics (14-16). Midazolam is currently known as an opioid with analgesic and antianxiety effects (17). This drug is categorized in benzodiazepine pharmacologic class. It has the highest efficacy in the shortest possible time (30 to 60 seconds) (18). Pregabalin is known as a structural analogue of gamma-aminobutyric acid (GABA). It inhibits calcium receptors, which inhibits the release of neurotransmitters (e.g. glutamate and dopamine) (19). It also relieves pain and reduces anxiety and dependence on opioids (21 and 20). It is necessary to examine analgesic effect of new drugs (either alone or in combination with each other) given that a unique model and guideline are not given for controlling the pain of patients undergoing ESWL. Therefore, the present study aimed to compare the analgesic effect of two combinations of pregabalin-fentanyl and midazolam-fentanyl.

METHOD

This was a double-blind clinical trial. The license for scientific procedure was obtained from the ethics committee of Jahrom University of Medical Sciences. The participants consisted of 141 patients visiting the lithotripsy unit in Peymani Hospital in Jahrom Town. The simple sampling method was used to select the participants. Inclusion criteria were 20<age<50, ASA I and ASA II, consent of the patients to participate in the project, 8mm<stone size<20mm. Exclusion criteria were 20kg/m2<BMI<30kg/m2, history of mental disorders, history of cardiovascular diseases, history of respiratory diseases, bleeding disorders, peptic ulcer, active

urinary tract infection, addition to analgesics and opioids and uncooperative patients. Past medical history of the patients was collected and a complete physical examination was performed. The baseline serum tests were taken, namely sodium, potassium, total blood count, coagulation, renal function tests (blood urea nitrogen and creatinine), full urine test and urine culture. Those who were not eligible for the study were excluded from the project. One microgram per kilogram fentanyl was administered intravenously and 300mg pregabalin was given orally to the patients ten minutes before the surgery in the first group (pregabalin-fentanyl and n = 47). One microgram per kilogram fentanyl and one microgram per kilogram midazolam were injected intravenously to the patients ten minutes prior to operation in the second group (fentanyl-midazolam and n = 46). Then, lithotripsy was performed with fluoroscopic projections in a standard manner in a supine position using Arian device in both groups. The severity of pain was measured every 20 minutes during the operation and two hours after the operation with the Visual Analog Scale for Pain (VAS Pain). The severity of pain was categorized into three classes, namely mild, moderate and severe. The severity of pain was scored as painless=0, 1< mild pain< 30, 30<moderate pain<70 and severe pain>70. Then, the patients were followed-up within two hours after the operation. The collected data was analyzed using SPSS version 21. Descriptive statistics (mean, standard deviation and percentages) and analytical statistical tests (Mann-Whitney and Chi-square) were used to analyze the data

FINDINGS

The mean age of the patients was 43.80 ± 13.71 in the first group (pregabalin + fentanyl)and 39.0 ± 11.19 in the second group (midazolam + fentanyl). Chi-square test results were matched in terms of age, gender, number of shocks and size of the stone (Table 1).

Table 1. Comparison of the two groups in terms of demographic factors

Group				
Factor		Fentanyl + midazolam (n=46)	pregabalin + fentanyl (n=47)	p-value
Gender[1]	Male	33 (71.7)	28 (59.6)	0.217
	Female	13 (28.3)	19 (40.4)	
Age[2]		39.0±11.19	43.80±13.71	0.140
The number of shockwaves2		2741±289.5	2721±320.96	0.411
The stone size2		12.36±4.24	12.35±3.81	0.923

[1] Frequency (percent)

[2] Mean ± standard deviation

The Mann-Whitney test results showed a significant difference between pregabalin-fentanyl and midazolam-fentanyl groups in terms of pain score in 20 minutes and 2 hours after drug administration (p-value <0.05) (Table 2).

Table 2. Comparison of pain score in ESWL in pregabalin + fentanyl and midazolam + fentanyl groups

Group			
Factor	Midazolam + fentanyl (n=46)	pregabalin + fentanyl (n=47)	p-value
Before drug administration	0(1-0)	0(1-0)	0.084
After 20min	0(0-0)	3(3-3)	0.00
After 40min	0(1-0)	3(3-3)	0.00
After 1h	0(0-0)	3(3-3)	0.00
After 2h	0(1-0)	3(3-3)	0.00
p-value	0.00	0.00	

Median (Q3-Q1)

Twenty minutes after taking the drug, 43 patients (91.5%) experienced severe pain, 2 patients (4.3%) experienced mild pain in the first group (pregabalin + fentanyl). However, 38 patients

(82.6%) were painless and 5 patients (10.9%) experienced mild pain in the second group (midazolam + fentanyl). Forty minutes after taking the drug, 43 patients (91.5%) experienced severe pain and 2 patients (4.3%) were painless in the first group. However, 30 patients (65.2%) patients were painless and 10 patients (21.7%) experienced mild pain in the second group. One hour after taking the drug, 44 patients (93.6%) experienced severe pain and 2 patients (4.3%) were painless in the first group. However, 39 patients (84.8%) were painless and 4 patients (8.7%) experienced mild pain in the second group. Two hours after taking the drug, 37 patients (78.7%) experienced severe pain and 6 patients (12.8%) experienced moderate pain in the first group. However, 25 patients (54.3%) were painless and 12 patients (26.1%) experienced mild pain in the second group (Table 3).

Table 3. Frequency of severity of pain in ESWL in pergabalin + fentanyl and midazolam + fentanyl groups

		Fentanyl + midazolam (n=46)		pregabalin + fentanyl (n=47)	
		Number	Percent	Number	Percent
Before drug administration	Painless	27	58.7%	35	74.5%
	Mild pain	15	32.6%	11	23.4%
	Moderate pain	3	6.5%	1	2.1%
	Severe pain	1	2.2%	0	0.0%
After 20min	Painless	38	82.6%	2	4.3%
	Mild pain	5	10.9%	2	4.3%
	Moderate pain	3	6.5%	0	0.0%
	Severe pain	0	0.0%	43	91.5%
After forty minutes	Painless	30	65.2%	2	4.3%
	Mild pain	10	21.7%	1	2.1%
	Moderate pain	4	8.7%	1	2.1%
	Severe pain	2	4.3%	43	91.5%
After one hour	Painless	39	84.8%	2	4.3%
	Mild pain	4	8.7%	1	2.1%

	Moderate pain	2	4.3%	0	0.0%
	Severe pain	1	2.2%	44	93.6%
After two hours	Painless	25	54.3%	4	8.5%
	Mild pain	12	26.1%	0	0.0%
	Moderate pain	5	10.9%	6	12.8%
	Severe pain	4	8.7%	37	78.7%

DISCUSSION

ESWL is the first line treatment for the patients with upper urinary tract stones. The patients treated with ESWL still complain about their pain despite invention of new generation of ESWL. Therefore, is necessary to use analgesics to relieve pain in the patients more easily. Simple painkillers, opioids and non-steroidal anti-inflammatory drugs are the most important drugs used so far. However, the effectiveness of these drugs is relative. No certain guideline is also given for prescription of these drugs (22). The results of this study showed that combination of midazolam and fentanyl is more effective in reducing the severity of pain in the patients undergoing ESWL than pregabalin-fentanyl combination. The results of this study are consistent with the results of other studies. Some of these studies are mentioned here. For example, Zeyneloglu et al. (2008) also aimed to compare analgesic and soothing effect of midazolam-fentanyl combination and dexmedetomidine in the patients undergoing ESWL. Most of the patients in the control (midazolam-fentanyl) were more satisfied with their medication, more relieved and painless than the intervention group (dexmedetomidine) during the surgery (23). Yang et al. (2002) compared the effect of midazolam-fentanyl and midazolam-ketorolac combinations for controlling pain in the patients undergoing ESWL. They showed that both combinations are effective in pain relief but the combination of midazolam- ketorolac has less side effects (24). Action mode of midazolam-fentanyl combination is interpreted in the below. Fentanyl and midazolam are opiate and sedative drugs. These drugs act on the central nervous system, increase the levels of endorphins and eliminate pain1 in the patients undergoing ESWL (25). Kalni et al. (2016) also compared the effect of midazolam and melatonin in controlling pain in the patients undergoing ESWL. The

severity of pain in the patients receiving midazolam is significantly less than those receiving melatonin (26). According to the results of the above-mentioned studies, the combination of midazolam and fentanyl has less side effects and is highly efficient in controlling pain in the patients undergoing ESWL. It can also be used for pain relief in outpatient ESWL. Some evidence suggests that the patients receiving GABA analogs (e.g. pregabalin and gabapentin) require less painkillers during the operation and these analogs relieve pain for a longer time. However, the results of the present study showed that pregabalin in combination with fentanyl does not reduce the severity of pain in the patients undergoing ESWL. Radmehr et al. (2017) also compare the analgesic effect of pregabalin and melatonin in the patients undergoing ESWL. The severity of pain increased during and after the operation in the patients given placebo, melatonin, and pregabalin. No significant difference was found between the three groups (27). Therefore, GABA analogs alone are not enough to relieve pain in patients. It is recommended to use different doses of this combination to achieve different results. On the other hand, the number of patients with higher than average pain in the midazolam-fentanyl group was less than the pregabalin-fentanyl group. In other words, the patients receiving midazolam-fentanyl experienced less pain than the group receiving the combination of pregabalin and fentanyl. Mehrabi et al. (2011) also aimed to compare the efficacy and side effects of fentanyl opiate drug and pethidine and midazolam combination for controlling pain during ESWL. They showed that more people experienced higher than average severity of pain in the pethidine-midazolam group compared to the fentanyl group (25).

CONCLUSION

The results of this study showed that less people experienced higher than average severity of pain in the group receiving midazolam-fentanyl compared to the group receiving pregabalin-fentanyl. It can be deduced that fentanyl in combination with midazolam has a greater efficacy in controlling pain in the patients undergoing ESWL. Therefore, it is recommended to use this combination to control pain in outpatients ESWL.

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