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Research Article

Comparison of Analgesic Effect of Fentanyl and Pregabalin-Fentanyl Combination in the Patients Undergoing Extracorporeal Shock Wave Lithotripsy: A Double-blind Clinical Trial

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ABSTRACT:

Background and Objective: Extracorporeal Shock Wave Lithotripsy (ESWL) is the first line treatment for upper urinary tract stones. Different analgesicssuch as opioids and nonsteroidal anti-inflammatory drugs (NSAIDs) werealready used for controlling the pain in the patients treated with this method but the efficacy of these drugs has not been determined yet. Therefore, the present study aimed to compare the effect analgesic of fentanyl andpregabalin-fentanyl combination in relieving pain in the patients treated with ESWL.

Materials and Methods: This was double-blind clinical trial on 141 patients visiting Lithotripsy Unit in Peymaniyeh Hospital in Jahrom Town. The patients were selected using a simple sampling method. Inclusion criterion was8mm < kidney stone < 20mm. Exclusion criteria were20 kg/m2 <body mass index (BMI) < 30 kg/m2, ahistory 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 was injected intravenously to the patients ten minutes prior to operation in the second group (fentanyl and n = 49). 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 usingthe 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: mean age of the participants in the first group was 43.80 ± 13.71 and 45.47 ± 16.32 in the second group. The two groups were matched in terms of age, gender, number of wave shocks and the size of kidney stones. The Mann-Whitney test results showeda significant difference between the first and second groups in terms of pain score from the first 20 minutes to 2 hours after drug administration. In other words, the severity of pain significantly increased in the first group and significantly decreased in the second group prior to operation and two hours after the operation (p-value < 0.05).

Conclusion: The results of this study showed that fentanyl was more effective than combination of pregabalin and fentanyl in relieving pain in the patients treated with ESWL.

Keywords: fentanyl, pregabalin, extracorporeal shock wave lithotripsy, pain

INTRODUCTION

Kidney stones are a common disease that is rising in the world (1). The risk of kidney stones in men and women is 13% and 7% respectively. The disease is most frequently seen in the third, and fourth decades of life (2).Much progress has been made in the last several decades in improving therapy of stone disease. Laser removal, Percutaneous Nephrolithotomy (PCNL), Transurethral Lithotripsy (TUL) and the uniqueExtracorporeal Shockwave Lithotripsy (ESWL) canbe mentioned as the techniques used for treatment of kidney stones (3). ESWL is currently a selective method for treatment of kidney stones (4). ESWL aims to break down the kidney stonesinto small pieces that can more easily travel through the urinary tract and pass from the body.In this technique, the kidney stone is targeted by externally produced shock waves that can propagate through the body (5). The patients treated with this method frequently experience pain caused by renal tissue damage due to low-frequency sound waves (6).Relieving pain during ESWL not only soothes the patients, but alsofacilitates the operation and increases the chance of successful treatment. This is because relieving pain reduces movement of kidney stone to accurately target the stone (9-7).Several studies have investigated analgesic effect of non-steroidal anti-inflammatory drugs (paracetamol and opioids) in ESWL. Certainly, eachdrug reduced pain in patients at different levels (10-12).Fentanyl is an opiate drug used as an analgesic in ESWL. It also has several side effects including respiratory disorders, sleepiness, nausea and vomiting (13).Pregabalin is a structural analogue of gamma-aminobutyric acid (GABA). Action mode of this analogue is binding to calcium receptors and inhibiting release of such neurotransmitters as glutamate and dopamine (14). Therefore, itcan relievepostoperative pain in patients. It also reduces opioid dependence and anxiety in patients (15 -16).There is no consensus on selecting the most effective drug for reducing pain in the patients treated with ESWL.Therefore, the present study aimed to compare the effect of fentanyl with fentanyl-pregabalin combination in reducing pain in the patients treated with ESWL.

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 Peymanieh 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 were20kg/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 was injected intravenously to the patients ten minutes prior to operation in the second group (fentanyl and n = 49). 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. 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 participants in the first group (pregabalin + fentanyl) was 43.80±13.71 and 45.47±16.32 in the second group (fentanyl). Chi-square test results were matched in the first and second groups in terms of age, gender, number of shockwaves and size of the stone (Table 1).

Table 1 - Comparison of two groups in terms of demographic factors

Group				
Factor		Fentanyl (n=49)	pregabalin + fentanyl (n=47)	p-value
Gender	Male	32 (65.3)	28 (59.6)	0.562
	Female	17 (34.7)	19 (40.4)	
Age		45.47±16.32	43.80±13.71	0.771
The number of shockwaves		2728±232.7	2721±320.96	0.458
The stone size		11.24±3.27	12.35±3.81	0.191

Mean ± standard deviation, frequency (percent)

The Mann-Whitney test results showed a significant difference between the first and the second groups in pain score in 20 minutes and two hours after drug administration (p-value<0.05) (Table 2).

Table 2 - Comparison of Pain score in ESWL in the pregabalin + fentanyl and fentanyl groups

Group			
Factor	Fentanyl (n=49)	pregabalin + fentanyl (n=47)	p-value
Before drug administration	0(1-0)	0(1-0)	0.660
After 20min	0(0-0)	3(3-3)	0.00
After 40min	0(0-0)	3(3-3)	0.00
After 1h	0(0-0)	3(3-3)	0.00
After 2h	0(0-0)	3(3-3)	0.00
p-value	0.037	0.00	

Median (Q3-Q1)

Twenty minutes after taking the drug, 43 patients (91.5) experienced severe pain in the first group (pregabalin + fentanyl) and 2 patients (4.3%)had no pain. However, 8 patients (16.3%) experienced mild pain and 40 patients (81.6%) were painless in the second group (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, 3 patients (6.1%) experienced mild pain and 46 patients (93.9%) were painless 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, 3 patients (6.1%) experienced mild pain and 46 patients (93.9%) were painless 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, 4 patients (8.2%) experienced moderate pain and 41 patients (83.7%) experienced no pain in the second group (Table 3).

Table 3 - Frequency of severity of pain in ESWL in pregabalin + fentanyl and fentanyl groups

		Fentanyl (n=49)		pregabalin + fentanyl (n=47)	
		Number	Percent	Number	Percent
Before drug administration	Painless	35	71.4%	35	74.5%
	Mild pain	11	22.4%	11	23.4%
	Moderate pain	2	4.1%	1	2.1%
	Severe pain	1	2.0%	0	0.0%
After 20min	Painless	40	81.6%	2	4.3%
	Mild pain	8	16.3%	2	4.3%

	Moderate pain	1	2.0%	0	0.0%
	Severe pain	0	0.0%	43	91.5%
After one hour	Painless	46	93.9%	2	4.3%
	Mild pain	3	6.1%	1	2.1%
	Moderate pain	0	0.0%	0	0.0%
	Severe pain	0	0.0%	44	93.6%
After two hours	Painless	41	83.7%	4	8.5%
	Mild pain	1	2.0%	0	0.0%
	Moderate pain	4	8.2%	6	12.8%
	Severe pain	3	6.1%	37	78.7%

DISCUSSION

ESWL is a safe, highly efficient treatment method for upper urinary tract stones. Many patients treated with this method experienced unpleasant feelings and pain (17). Various drugs have been already prescribed to reduce pain in the patients treated with ESWL but a highly efficient analgesic have not been selected yet. The results of this study showed a significant reduction in the severity of pain in the fentanyl group before intervention and up to two hours after intervention. In other words, the results of the present studyshowed that fentanyl alone has greater analgesic effect than the pregabalin-fentanyl combination. Mitsogiannis et al. (2008) also aimed to compare the effects of fentanyl citrate and parecoxib sodium in relieving pain in the patients undergoing ESWL.Similar to the results of this study, the results of the former study showed that fentanyl citrate and parecoxib sodium relieve pain in 90% and 17.8% ofthe patients respectively (18). Fentanyl, pethidine and midazolam are all opiate and sedative drugs that act on the central nervous system, increase levels of endorphins and eliminate pain1 (19). El sayed et al. (2015) showed a significant increase in the severity of pain in the fentanyl-ketamine group compared to ketamine-dexmedetomidine group(20). These results are not consistent with the results of this study. The combination of fentanyl with ketamine can justify these confounding results. In other words, fentanyl in combination with other drugs does not exhibit desirable analgesic effects. The results of this study also showed a significant increase in the severity of pain before intervention an up to two hours after the intervention in the pregabalin-fentanyl group. Rademehr et al. (2017) compared analgesic effect of pregabalin and melatonin in the patients treated with ESWL. Similar to the results of this study, the results of the former study showed that the severity of pain has increased in the two groups before the intervention and up to one hour after the surgery (21). Atef et al. (2014) showed that severity of pain was not significantly related to medication in the patients undergoing lower back surgery2 treated with placebo, pregabalin, melatonin and pregabalin-melatonin combination (22). However, pregabalin in combination with fentanyl did not show the same effect in the present study. Yang et al. (2002) also showed that the combination of midazolam-fentanyl reduce pain in the patients undergoingESWL. The results of the former study were not consistent with the results of the above-mentioned studies (23). Some scientific evidence suggests thatGABA analogues (e.g. pregabalin and gabapentin) can be used to relieve pain in the patients (24). However,pregabalin-fentanyl combinationdid not exhibit an acceptable analgesic effect in the present study. The number of the people with higher than average pain in the pregabalin-fentanyl group was more than the fentanyl group. In other words, the patients treated with fentanyl experienced less pain than those treated with pregabalin-fentanyl combination. Mehrabi et al. (2011) also aimed to compare the efficacy and side effects of low-dose fentanyl (50 micrograms) opiate drug and pethidine-midazolam combination in pain management

during ESWL. They showed that the frequency of painless patients and those with mild pain in the intervention group (fentanyl) and the frequency of severe pain in the control group (combination of pethidine and midazolam) were higher (19). These results were consistent with the results of this study. Zeyneloglu et al. (2008) also showed that most patients treated with midazolam-fentanyl combination experience less pain than those treated with dexmedetomidine (25).

CONCLUSION

The results of this study showed greater efficacy of fentanyl in pain management in the patients treated with ESWL in comparison with pregabalin-fentanyl combination. It can be deduced that administration of fentanyl alone has a greater analgesic effect. Therefore, it is recommended that this drug be used to control paininoutpatient ESWL.

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