

Research Article

A Comparison of the Effects of Fentanyl and Midazolam-Fentanyl on the Pain Control in Patients Undergoing Extracorporeal Shock Wave Lithotripsy: A Double-Blind Clinical Trial

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ABSTRACT:

Background and objective: Despite the production of a new generation of extracorporeal shock wave lithotripters, this treatment is still accompanied by pain experience in patients. Therefore, it is necessary to use appropriate painkillers to control the pain of patients and achieve the highest efficiency in extracorporeal shock wave lithotripsy. Hence, the present study aimed to compare the effects of fentanyl and midazolam-fentanyl on the pain control in patients undergoing extracorporeal shock wave lithotripsy.

Materials and methods: A double-blind clinical trial was conducted on 141 patients visiting the lithotripsy ward of Peymaniyeh Hospital of Jahrom who were selected based on the convenience sampling method. The main inclusion criterion was the stone size of 8-20 mm and the exclusion criteria were a BMI of less than 20 or greater than 30 per square meter, a history of mental disorders, and addiction to analgesics and opiates. The subjects were randomly assigned to two groups; the first group (midazolam-fentanyl, n=46) intravenously received 1 µg/kg of fentanyl and 1 µg/kg of midazolam 10 minutes before the procedure and the second group (fentanyl, n=49) was treated with only 1 µg/kg of fentanyl in the same way. Then, lithotripsy was performed for both groups in a standard manner and the pain severity was measured every 20 minutes during the procedure and up to 2 hours after the procedure using the Visual Analogue Scale (VAS). The obtained data were statistically analyzed using descriptive statistics (mean, standard deviation, and percentages) and inferential statistics (Mann-Whitney U and Chi-square) in SPSS-21.

Results: The mean age of subjects in the first (midazolam-fentanyl) and second (fentanyl) groups was equal to 39.00±11.19 and 45.47±16.32, respectively. The two groups were matched in terms of intervening factors. The results showed that there is a significant difference between the two groups in the pain score at 40 minutes and 2 hours after the administration ($p < 0.05$). In addition, the number of subjects with a pain severity above the average at 40 minutes and 2 hours after the administration was fewer in the second group.

Conclusion: The study results indicated that fentanyl has managed to control pain in patients undergoing extracorporeal shock wave lithotripsy more effectively than midazolam-fentanyl.

Keywords: Fentanyl; Midazolam; Pain; Extracorporeal shock wave lithotripsy

INTRODUCTION:

The formation of urinary tract stones is considered an old disease in humans and it a long time that humans have been fighting this

disease [1]. The stone formation process occurs when the urine converts into an over-saturated solution. In other words, the urinary matters

exceed their permissible level. These changes eventually lead to the formation of crystals and sedimentation of the urinary matters [2]. Often, the composition of urinary stones includes calcium (calcium oxalate and calcium phosphate) with a prevalence of 84% [3] and other types of stones such as uric acid with a prevalence of 7-12%, infectious stones (struvite) with a prevalence of 4-11%, cysteine stones with a prevalence of less than 1%, and others with a very low prevalence (zantin and dihydroxyadenine) [3, 4, 5]. The prevalence of this disease is estimated to be between 1-15% throughout the entire life of humans, which may vary depending on some demographic variables such as age, gender, and geographical area. The risk of this disease is approximately 13% in men and is 7% in women [6]. Nowadays, extracorporeal shock wave lithotripsy has become a safe method to manage and treat the upper urinary tract stones, because this method is non-invasive and easy to perform [7]. Patient cooperation during the procedure leads to the accurate detection of the stone location. Therefore, it is very important to correctly choose the painkillers for administration to these patients. The correct selection of drugs makes patients have less pain and mobility during the procedure and, as a result, targeting and fragmentation of stones will be more successful [8]. Anesthetic methods have changed from general or local anesthesia to pain relief techniques [9]. Several medications including steroid anti-inflammatory drugs (ketorolac or diclofenac), opioids (pethidine, morphine, and fentanyl), and other anesthetic techniques (skin creams or topical anesthetics) have been used in this regard [10]. Fentanyl is considered an industrial narcotic with a rapid onset of effect and a short length of effect. Since this drug is a strong agonist for μ -opioid receptors, it is commonly used in shock lithotripsy and causes a tolerable level of pain in patients undergoing this procedure [11]. On the other hand, it has been observed that midazolam, a drug from the benzodiazepines category, is used to reduce pain with fast efficiency, short recovery time, and minimum side effects [12]. Until now, there is no specific treatment to control the pain of

patients undergoing extracorporeal shock wave lithotripsy. Hence, the present study aims to compare the effects of fentanyl and midazolam-fentanyl on the pain control in these patients.

MATERIALS AND METHODS:

After obtaining the necessary permissions from the Ethics Council of Jahrom University of Medical Sciences, a double-blind clinical trial was conducted on 141 visiting the lithotripsy ward of Peymaniyeh Hospital of Jahrom who were selected based on the convenience sampling method. The inclusion criteria were being aged 20-50, being in class 1 or 2 of American Anesthesiology Association, the stone size of 8-20 mm, and patient's willingness to participate in the study. The exclusion criteria also included a BMI of less than 20 or greater than 30 per square meter, a history of mental disorders, cardiovascular and respiratory diseases, bleeding disorders, peptic ulcer, and active urinary tract infection, addiction to analgesics and opiates, and inability to cooperate with the researcher. The history of patients was recorded and all physical examinations, basic serum test (including sodium, potassium, and total blood count), coagulation tests, kidney function tests (blood urea nitrogen and creatinine), and urine test and culture were performed for all subjects. After eliminating the patients who did not meet the inclusion criteria, the remaining 95 subjects were randomly assigned to 2 groups; the first group (midazolam-fentanyl, n=46) intravenously received 1 μ g/kg of fentanyl and 1 μ g/kg of midazolam 10 minutes before the procedure and the second group (fentanyl, n=49) was treated with only 1 μ g/kg of fentanyl in the same way. Then, lithotripsy was performed for subjects of both groups in the supine position by Arian Lithotripter. The pain severity was measured every 20 minutes during the procedure and up to 2 hours after the procedure using the Visual Analogue Scale (VAS). Based on patients score on VAS, they were classified into four groups of no pain (a score of 0), mild (1-30), moderate (30-70), and severe (more than 70). The obtained data were statistically analyzed using descriptive statistics (mean,

standard deviation, and percentages) and inferential statistics (Mann-Whitney U and Chi-square) in SPSS-21.

Findings:

The mean age of subjects in the first (midazolam-fentanyl) and second (fentanyl)

groups was equal to 39.00±11.19 and 45.47±16.32, respectively. The results of Chi-square test showed that subjects of the two groups were matched in terms of age, gender, number of shocks, and size of stone (Table 1).

Table 1: Comparison of the two groups in terms of demographic variables

Variable		Group		p-value
		midazolam-fentanyl (n=46)	Fentanyl (n=49)	
Gender	Male	33(71.7)	32(65.3)	0.500
	Female	13(28.3)	17(34.7)	
Group		39.0±11.19	45.47±16.32	0.094
Number of shocks		2741.3±289.5	2728.6±232.7	0.813
Size of stone ²		12.36±4.24	11.24±3.27	0.227

The results of Mann-Whitney U indicated that there is a significant difference between the two groups in the pain core at 40 minutes and 2 hours after the administration ($p<0.05$).

Table 2: Comparison of the two groups in terms of the pain score during extracorporeal shock wave lithotripsy

Variable	Group		p-value
	midazolam-fentanyl	fentanyl	
Before giving the medication	0(1-0) ¹	0(1-0)	0.205
First 20 minutes	0(0-0)	0(0-0)	0.987
40 minutes	0(1-0)	0(0-0)	0.001
An hour after	0(0-0)	0(0-0)	0.134
Two hours after	0(1-0)	0(0-0)	0.007
p-value	0.00	0.037	

Median (Q3-Q1)

In the first group (midazolam-fentanyl), 30 subjects (65.2%) felt no pain and 10 of them (21.7%) experienced a mild pain at 40 minutes after the drug administration. In the second group (fentanyl), 46 patients (93.9%) felt no pain and only 3 of them (6.1%) underwent a mild pain at the same time. At 2 hours after the drugadministration, 25 patients (54.3%) in the first group felt no pain and 12 of them (26.1%) had a mild pain. In addition, 41 patients (83.7%) in the second group felt no pain and 4 of them (8.2%) experienced a moderate pain at the same time. According to the results, the number of subjects with a pain severity above the average at 40 minutes and 2 hours after the drug administration was fewer in thesecond group (Table 3).

Table 3: Frequency of pain levels during extracorporeal shock wave lithotripsy in the two studied groups

		midazolam-fentanyl		fentanyl	
		Number	Percentage	Number	Percentage
Before the administration	Painless	27	58.7%	35	71.4%
	Mild pain	15	32.6%	11	22.4%
	Moderate pain	3	6.5%	2	4.1%
	Severe pain	1	2.2%	1	2.0%
20 minutes after the administration	Painless	38	82.6%	40	81.6%
	Mild pain	5	10.9%	8	16.3%
	Moderate pain	3	6.5%	1	2.0%
	Severe pain	0	0.0%	0	0.0%
40 minutes after the administration	Painless	30	65.2%	46	93.9%
	Mild pain	10	21.7%	3	6.1%
	Moderate pain	4	8.7%	0	0.0%

	Severe pain	2	4.3%	0	0.0%
One hour after the administration	Painless	39	84.8%	46	93.9%
	Mild pain	4	8.7%	3	6.1%
	Moderate pain	2	4.3%	0	0.0%
	Severe pain	1	2.2%	0	0.0%
Two hours after the administration	Painless	25	54.3%	41	83.7%
	Mild pain	12	26.1%	1	2.0%
	Moderate pain	5	10.9%	4	8.2%
	Severe pain	4	8.7%	3	6.1%

DISCUSSION:

High severity of pain during extracorporeal shock wave lithotripsy can increase the mobility of patients and also their respiratory movements. These two events lower the accuracy of stones fragmentation and cleansing. Moreover, they cause waste of energy in the shock lithotripter and increased number of shocks, which can result in increased rate of kidney hemostasis and blood pressure. Evidence shows that despite the production of a new generation of extracorporeal shock wave lithotripters, this treatment is still accompanied by pain experience in patients. Therefore, it is necessary to use appropriate painkillers to control the pain of patients and achieve the highest efficiency in extracorporeal shock wave lithotripsy [13]. The results of the present study demonstrated that fentanyl has been more effective than midazolam-fentanyl in controlling the pain of patients undergoing extracorporeal shock wave lithotripsy. Fentanyl significantly reduced the pain score of patients at 40 minutes and 2 hours after the procedure. Mitsogiannis *et al.* (2008) compared the effects of fentanyl citrate and parecoxib sodium on the pain relief in patients undergoing extracorporeal shock wave lithotripsy and observed that these two drugs caused pain relief in 90% and 17.8% of patients, respectively [14]. Fentanyl, pethidine, and midazolam all are among the opiates and sedative drugs that affect the central nervous system and thereby increase the level of endorphin and relieve pain [15]. In a study conducted by El-Sayed *et al.* (2015), the pain severity significantly increased in the fentanyl-ketamine group compared to the dexmedetomidine-ketamine [16], which is not consistent with the findings of the present study. The combination of fentanyl with ketamine can

somehow justify this difference. In other words, the analgesic effect of fentanyl reduces in combination with other drugs. Zeyneloglu *et al.* (2008) compared the effects of dexmedetomidine and midazolam-fentanyl on the pain relief in patients undergoing extracorporeal shock wave lithotripsy and observed that most patients in the control group (midazolam-fentanyl) had a very high degree of satisfaction with the severity of the pain they tolerated (83%) compared to those treated with dexmedetomidine (56%) ($p=0.038$) [17]. The number of subjects with a pain severity above the average at 40 minutes and 2 hours after the administration in the midazolam-fentanyl group was higher than the fentanyl group. This means that the subjects who received midazolam-fentanyl experienced higher pain than those treated with only fentanyl. Mehrabi *et al.* (2011) compared the efficiency and side effects of fentanyl at a low dose (50 µg) and the combination of pethidine and midazolam in the pain control during extracorporeal shock wave lithotripsy and reported that the highest frequency of “no pain” and “mild pain” was related to the intervention group (fentanyl) and the highest frequency of “severe pain” belonged to the control group (combination of pethidine and midazolam) [18]. Similarly, Raki and Al-Hashemi compared the analgesic effect of dexmedetomidine and morphine with the combination of midazolam-tramadol in patients undergoing the same procedure and reported that the pain score (VAS) in the dexmedetomidine group was lower than that of the midazolam-tramadol group [19]. However, it has been reported that midazolam can have the effects different from those of the present study. Kalani *et al.* (2016) compared the analgesic effect of midazolam and melatonin in patients

undergoing extracorporeal shock wave lithotripsy and observed that the pain severity was significantly lower in the midazolam group [20]. Therefore, it can be concluded that midazolam alone and without combination with other drugs can effectively reduce the pain of patients.

CONCLUSION:

The study results indicated that fentanyl has managed to control pain in patients undergoing extracorporeal shock wave lithotripsy more effectively than midazolam-fentanyl. Therefore, the combination of fentanyl with another drug did not produce satisfactory results in this study. Hence, it is recommended to study the analgesic effect of fentanyl in combination with other painkillers in order to help patients undergoing extracorporeal shock wave lithotripsy feel less pain and increase the success rate of lithotripsy procedure.

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