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Use of Fentanyl Patch and Intravenous Morphine for Treatment of Leg Bone Fracture: Treatment Profile, and Clinical Effectiveness

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Abstract

BACKGROUND: Severe pain is one of the major problems in patients with leg bone fracture. Various methods have been proposed to relieve pain. Opioids are one of the most important available medications to control these types of pain. Among the opioids available, fentanyl can be applied for its unique properties as transdermal patches.

AIM: Therefore, the current study aimed to investigate the effect of intravenous morphine and fentanyl skin patch in patients with a lower leg fracture.

METHODS: We entered 60 patients in this randomised, one-blind randomised clinical trial among patients referring to the emergency department of Vali-e-Asr Hospital in Arak with a fracture of the leg. Demographic and clinical data were recorded for patients. The case group (n = 30) received the fentanyl patch in the same area. Patients in the control group (30) received 0.1mcg/kg of morphine intravenously. In both groups, the severity of pain was measured every 20 minutes within two hours after onset of treatment based on VAS criteria and subsequently recorded in the checklist. Data were analysed by SPSS v.22 software package.

RESULTS: The results of the present study demonstrated that the mean visual analogue scale (VAS) pain score at minutes 20, 40, 60 and 80 were statistically lower in intervention group when compared with the control group (p = 0.000).

CONCLUSION: Our results indicated a considerable risk-benefit profile for the treatment of pain in patients suffering from dysphagia, nausea and vomiting, or resistance to other opioids. The use of fentanyl patch is also suitable for patients who are not able to take their medication at their scheduled time.

Introduction

The increasing use of machinery and vehicles has led to vehicle-*related accidents* and serious physical *injuries*, which has become a major health problem for humans. Due to the occurrence of accidents at high speeds, vehicle-*related injuries* are a considerable risk *of* provoking a severe complication and often results in disability, amputation and death of the injured patients. One of the most common causes of amputation is open fractures, one of the most common causes of amputation is open fractures, most commonly occurring in the legs of 21.9% [1] and consisting 25% of open fractures [2].

On the one hand, the type of soft tissue injury causes acute and life-threatening infections in open fractures; on the other, creates chronic and resistant bone infection [3]. Leg bone fractures (tibia and fibula fractures) are the most common bone fracture in the body that occurs in the majority of men at younger ages [4], due to the low soft tissue coverage in anterior and *anteromedial parts* and inadequate blood supply and soft tissue in this area [5]; whereas tibia

nonunion account for the highest percentage of total referrals [6]. Pain is one of the most preventable complications in surgeries, but usually, it is not enough to treat it. Pain can indirectly increase morbidity and mortality, while also contributing to increased costs and lower quality of life.

Pain relief is a challenge after surgery, which requires pain relievers with minimal side effects and the highest level of safety for the patient [7]. Currently, postoperative pain treatment has been highly considered. Some studies have reported a high prevalence of postoperative pain. Severe pain not only causes pain and discomfort but also prevent patients from returning to daily activities, which is considered an important socio-economic factor [8].

Severe pain is one of the major problems for patients with leg bone fracture. Various methods have been proposed to relieve pain associated with bone fracture. Opioids can be mentioned as the most important compounds with *the most availability* regarding *controlling* this type of pain. Pain control using oral and intravenous opioids requires effective dosage and regular use of medications. In most cases, regular use of these compounds may be difficult due to problems with patient's problem and forgetfulness and ultimately leads to insufficient control of the patient's pain.

Therefore, various methods have been introduced for transferring the drug, which can be referred to transdermal adhesives [9]. Among the opioids available, fentanyl can be applied for its unique properties as transdermal patches (adhesives). Fentanyl has been considered as an artificial opioid due to its fatty properties and high analgesic power compared to morphine in the 1990s [10]. *Fentanyl transdermal* patch can be effectively used, especially for patients suffering from dysphagia, nausea and vomiting, or resistance to treatment, or intolerance to other opioids.

Also, this method is appropriate for patients who are not able to take their medication at the prescribed time [11]. Fentanyl is an artificial opiate drug that was first made in 1960 and has been used as part of the anaesthetic regimen for about 30 years. Physical properties of the drug include low molecular weight, high solubility in fat and high power, which has led to the use of fentanyl in *transdermal* drug delivery *systems* [12]. There is a controversy about the effectiveness of the fentanyl skin patch method, where some studies have not yet succeeded in exhibiting this effect well. The researchers attribute the causes of these differences to the differences in the methodology and quality of the studies, as well as sample sizes and comparison groups.

The current study aimed to compare the effectiveness of the *fentanyl transdermal patch* with the effect of intravenous morphine in patients.

Material and Methods

We enrolled 60 (43 man and 17 women) in this, *single-blind* randomised controlled *clinical trial*. The statistical population consisted of patients who referred to the emergency department of Vali-e-Asr Hospital in Arak, with a fracture of the leg. All of them were in the first and second classes (*ASA II and I*) of the American Society of Anesthesiologists (ASA). The primary diagnosis was based on four criteria including localised tenderness, pain, deformity, and crepitation. Patients were entered the treatment groups using a random number table after filling the inclusion criteria. The primary examination of the patient was done by a specialist, and the final diagnosis was performed by the two physicians. Early demographic and clinical characteristics of patients were recorded. The patients' pain was then checked by the VAS criteria and data recorded in the checklist.

In the case group (30 patients), subjects received the fentanyl transdermal patches in the same areas. The *patch placement* includes 1: left deltoid muscle; 2: right deltoid muscle; 3: left chest on the top of the nipple; 4: *right chest* on the top of the nipple.

In the control group (30 patients), subjects also received 0.1 mcg/kg of morphine intravenously.

In both groups, pain intensity was measured every 20 minutes during two hours after treatment based on VAS criteria and finally recorded in the checklist.

All data were analysed by SPSS v.22 software package. To present the results, mean indexes, standard deviation, standard error, the percentage of frequency were applied. Furthermore, tests such as covariance analysis, Chi-square, Independent T-test or its nonparametric equivalents were employed to compare the means. $P < 0.05$ was considered as statistically significant.

Inclusion criteria included the age of over 18 years, patients with leg fractures, *obtaining* an informed consent form,

Exclusion criteria include Patients' *refusal to participate* in the study, the failure to diagnose fractures in the radiographic images, the incidence of complications and the sensitivity to the drug administration, and the history of related diseases, as well as the transferring the patient to the operating room within two hours after entering the emergency room.

The informed consent of the participation in the study was taken optionally, and the confidentiality of the information was retained. This research project was approved by the Ethics Committee of the Research Council of Arak University of Medical Sciences with the number 2792 (ethics code: IR.ARAKMU.REC.1395.298).

Results

Of the 30 patients in the experimental group, 20 were men (66.6%) and the rest were women. Also, the control group consisted of 23 male patients (76.7%) and 17 female patients. To test the homogeneity of the two groups, Chi-square test was applied, where showed no significant difference in both groups (P = 0.22). In the test group, the majority of patients (73.3%) were in the age group of 21-30 years, while the lowest frequency (3. 3%) was in the age group of fewer than 20. Moreover, most of the patients in the control group (70%) were seen in the age group of 20-30 years, and the lowest (6.7%) belonged to the age group of fewer than 20 years old. Based on the Fisher test, the two groups did not exhibit a significant difference in age (P = 0.42). Base on the use of t-test, there was no significant difference between the mean *VAS* pain score at 0 minutes (P = 0.37) in both groups. There was no significant difference between the two groups regarding the vital signs of the patients (Table 1).

Table 1: Comparison of pain intensity and vital signs at zero minute

Variable	Fentanyl	Morphine	Analysis text
VAS	06.9±.66	8±.78	0.370
O2saturation	36.95±20.3	36.95±45.3	0.100
BP	63.13±25.1	73.13±15.1	0.710
T	37±.45	01.37±.13	0.09
RR	36.22±78.4	30.21±36.5	0.140
PR	53.98±60.9	90.95±45.3	0.140

Using t-test, the mean *VAS* pain score at 20 minutes in both groups was significantly different (P = 0.000). A pain score of the morphine group significantly decreased more than the other group. Furthermore, the vital signs of the patients in both groups were evaluated using a t-test, where the findings did not emphasise the significant difference between the two groups (Table 2).

Table 2: Comparison of pain severity and vital signs in the 20 the minute

Variable	Fentanyl	Morphine	Analysis text
VAS	54.8±.66	26.4±.69	0.000
O2saturation	23.96±27.1	23.96±47.1	0.640
BP	73.13±15.1	81.13±54.1	0.770
T	97.36±.17	37±.45	0.730
RR	40.22±78.4	40.22±52.4	1.000
PR	53.96±45.3	46.98±06.9	0.270

The mean *VAS* pain score in both groups was statistically significant at 40 minutes (P = 0.000); in other words, the mean *VAS* pain score of morphine group was markedly decreased as compared to another group. There was no significant difference between the two groups regarding O_2 saturation, RR and PR in both groups. However, we found that the mean of BP and T in both groups was statistically different from t-test (Table 3).

Table 3: Comparison of severity of pain and vital signs in 40 the minute

Variable	Fentanyl	Morphine	Analysis text
VAS	20.5±.92	21.4±.76	0.000
O2saturation	30.93±57.1	23.96±27.1	0.310
BP	24.12±01.5	86.13±49.1	0.000
T	99.36±.19	8.36±.24	0.002
RR	36.21±09.6	40.22±78.4	0.460
PR	20.96±72.3	53.98±06.9	0.190

As shown in Table 4, the mean pain score (VAS) of 60 minutes was lower in the morphine group than in the fentanyl group (P = 0.000). There was no significant difference between the two groups regarding O2saturation, RR, and PR symptoms in both groups. However, the mean values of P and T in both groups were significantly different based on the T-test.

Table 4: Comparison of the severity of pain and vital signs in the 60th minute

Variable	Fentanyl	Morphine	Analysis text
VAS	1.4±.75	16.3±.79	0.000
O2saturation	23.96±7.12	26.96±31.1	0.920
BP	21.12±91.2	91.13±4.1	0.001
T	97.36±.21	86.36±.22	0.005
RR	63.20±78.5	40.22±78.4	0.200
PR	83.95±.70	46.98±65.1	0.140

Table 5 demonstrated a significant difference between the mean *VAS* pain score at 80 minutes in both groups (P = 0.000). Also, there were no significant differences in O2 saturation, RR, and PR symptoms in both groups. However, the mean value of BP and T in both groups was remarkably different (Table 5).

Table 5: Comparison of pain severity and vital signs in the 80th minute

Variable	Fentanyl	Morphine	Analysis text
VAS	06.4±.73	23.3±.77	0.000
O2saturation	36.96±17.2	26.96±31.1	0.760
BP	11.12±68.2	76.13±46.1	0.002
T	97.36±.21	86.36±.22	0.005
RR	93.20±92.5	43.22±80.4	0.280
PR	9.96±89.3	46.98±06.9	0.170

As indicated in Table 6, the mean *VAS* pain score for 100th minutes in the fentanyl group was less than the other group (P = 0.000). On the other hand, there were no significant differences in the O2 saturation, RR, and PR in both groups. However, the mean value of BP and T in both groups revealed a significant difference by using t-test.

Table 6: Severity of pain and vital signs in the 100th minute

Variable	Fentanyl	Morphine	Analysis text
VAS	56.3±.50	13.4±.77	0.001
O2saturation	36.96±21.1	33.96±26.1	0.920
BP	44.12±40.2	89.13±48.1	0.000
T	96.36±.20	85.36±.23	0.005
RR	55.21±01.1	16.22±.89	0.620
PR	64.94±19.5	53.97±6.9	0.009

Our results revealed that the mean *VAS* pain score in the 100th minute in the fentanyl group was not significantly different compared with morphine

group (P = .000). We did not find a significant difference in the vital signs of O2 saturation, RR and PR in patients in both groups. Nevertheless, the mean values of BP and T in both groups were significantly different by using T-test (Table 7).

Table 7: Comparison of severity of pain and vital signs in 120 the minute

Variable	Morphine	Fentanyl	Analysis text
VAS	06.3±.36	03.4±.76	0.000
O2saturation	89.96±22.2	40.96±47.1	0.270
BP	42.12±45.6	82.13±24.5	0.000
T	94.36±.25	46.36±.22	0.050
RR	30.20±85.4	53.22±89.4	0.080
PR	10.95±17.4	60.98±08.9	0.060

We compared the mean *VAS* pain at minutes 0 to 120 in the two groups of fentanyl and morphine. The results exhibited that there was no significant difference between the two groups in only 0 minutes, but in the remaining minutes, this difference was statistically significant (Table 8).

Table 8: VAS pain score at minutes 0 to 120

Variable	Fentanyl	Morphine	Analysis text
VAS0	06.9±.66	8±.78	0.370
VAS20	54.8±.66	26.4±.69	0.000
VAS40	20.5±.92	21.4±.76	0.000
VAS60	1.4±.75	16.3±.79	0.000
VAS80	06.4±.73	23.3±.77	0.000
VAS100	56.3±.50	13.4±.77	0.001
VAS120	06.3±.36	03.4±.76	0.000

Discussion

In this clinical trial study, 60 patients were randomly divided into intervention and control groups during 2017 in Valiasr Hospital. The study showed that the oldest person in the intervention group was 94 years old, and the youngest was 49 years old. Moreover, the oldest person in the control group belonged to a 64 years old individual and the youngest person was 16 years old. Using statistical tests, the mean age of the two groups was not found to be significantly different (p = 0.42).

Furthermore, the mean height of the subjects in the intervention group was determined to be 6.2 ± 1.71. In the intervention group, the mean height of the patients was calculated as 15.60 ± 1.69. There was no statistically significant difference between the mean height of the control and intervention groups (p = 0.12). This study aimed to compare the pain in patients with fracture of the leg in the use of fentanyl skin patches and injectable morphine ampoule. Before the onset of the intervention, by comparing the pain with VAS scores, it was revealed that the mean score of pain in both groups was not significantly different (P-value = 37.7).

Regarding the random sampling and the similarity of pain between the two groups, the pain was accordingly the same between the two groups before each intervention. Based on the results presented in this study, the pain score between the two intervention and treatment groups was statistically significant at 20, 40, 60 and 80 minutes, so that the pain score of the control group (morphine) was lower than that of the intervention group (P = 0.000). In other words, morphine has been able to produce more analgesic effects at these times. The onset of analgesic effect of intravenous morphine (0.1-0.05 mg.kg) is 10-20 minutes after injection, but the onset of analgesic effect of fentanyl skin patch could be started after one hour [13].

Also, fentanyl patch is not predictable, which its effects may be started up to several hours, depending on the body temperature, and the previous dose of the drug, as well as other factors such as the location of use, hemodynamics and the general condition of the patient (fragility, hypovolemia).

Absorption continues for a few hours unpredictably *following* removal *of* the *patch* [14]. These results are consistent with our findings. Also, due to the slow start of fentanyl absorption, patients may use a patch from the day before surgery. Localised blood flow to the patch site can affect the absorption of the drug. Heat blankets, moisture or sepsis, can increase blood flow to the skin, leading to an increase in total systemic absorption [14]. The results of our study demonstrated that the mean score of pain at 100 and 120 minutes was significantly different, where the mean score of pain in the intervention group was significantly lower as compared to the control group (p = 0.00). In other words, patients in the intervention group who used fentanyl skin patch had less pain after one hour than those in the control group. The unique properties of fentanyl include its 75-fold strength compared to morphine, low molecular weight, and lipophilicity, as well as higher skin absorption capacity than morphine.

In*consistent with our* results, these features reduce pain by initiating the effect of fentanyl [15]. In 2004, Clark found that the analgesic effect of fentanyl skin patch was significantly higher than that of morphine [16], which is in agreement with our results. In another study by Hemmati et al., The results showed that fentanyl skin patch significantly reduced the pain of patients with soft tissue tumours compared to placebo [17]. Another study evaluated the safety and therapeutic effect of 12-month use with fentanyl patch. This mentioned study indicated a reasonable risk-benefit profile for managing moderate to severe chronic pain in non-cancer patients treated with fentanyl patch under long-term compared with patients who treated with other opiate drugs. Respiratory depression, drug dependence, and drug discontinuation were rarely observed in patients [18].

Some of the properties of the drug that leads to better tolerance of the drug by the patient, its effectiveness and its relative safety include the need

for repeated administration of the drug, lower *peak plasma concentration*, and lack of liver first pass metabolism [19]. In patients with cancer pain, the use of this drug leads to prolonged and effective analgesia. Four different drug types are available including 25, 50, 75 and 100 micrograms per hour.

The fentanyl patch needs 24 to 72 hours to reach a sustained level of blood, and absorption of remaining fentanyl lasts for several hours after removing the patch. After removing the fentanyl patch, it takes about 17 hours to reduce the plasma concentration of the drug by 50%. Therefore, there is a potential for drug interruption with anaesthetics, sleep apnea and other opioids several hours after removing the patch. Therefore, the risk of drug interruption is not eliminated immediately *following* the removal *of* the *patch*. It is worth noting that the fentanyl patch releases the drug for up to 72 hours and has been proposed as a synthetic drug with short-term analgesia [20].

On the other hand, fentanyl provides an appropriate plasma concentration up to 72 hours, where the blood concentration of the drug gradually increases, leading to a reduced risk of complications. Fentanyl metabolites are not pharmacologically active and are not affected by the liver first pass metabolism or gastrointestinal absorption. Fentanyl with a high tendency and specifically binds to the μ2-opioid receptor. Therefore, the side effects of activating the μ2-opioid receptor such as nausea, vomiting and constipation that is seen with the use of morphine are not seen with this drug. It should be taken into consideration that the complications of accumulation of metabolites are not seen in patients receiving this drug [21].

In summary, this study exhibited that the fentanyl skin patch has a significantly more analgesic effect in patients with fractures after one hour than morphine. The use of transdermal fentanyl is useful especially for patients suffering from dysphagia, nausea, vomiting, or other forms of resistance to other opioids. It is also suitable for patients who are not able to take their medication at their scheduled time.

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