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Transdermal Fentanyl in Hospitalized Patients with Severe Pain

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Summary

Approximately 28% of hospitalized patients have severe pain. Opioids are indicated in moderate to severe pain. Transdermal fentanyl (FT) has been used in severe acute pain.

Objective: To describe the evolution in pain intensity in patients with severe pain who received FT.

Material and Methods: Retrospective case series (March - July 2019), at the Specialty Hospital XXI Century National Medical Center Mexico City. Thirteen patients who received FT 25 µg/h participated. Pain intensity was assessed with the Analog Numerical Scale (ENA) at 0 (baseline = prior to the FT patch), 24, 48, 72 hours, and side effects. Descriptive statistics were applied for sociodemographic variables, Student's t-test to assess differences in pain intensity, considering a statistical significance of p 0.05.

Results: 5 (38.5%) women, 8 (61.5%) men, mean age 57 years were included. Distribution of pain type: postoperative 5 (38.5%), bone 4 (30.8%), arterial 3 (23.1%, 1 (7.7%) Lyme disease. The intensity of pain with ENA in times: 0, 24, 48, 72 hours was: Average: 0 = 8, 24 = 2, 48 = 3, 72 = 2, Rest: 0 = 8, 24 = 2.23, 48 = 2.69, 72 = 1.54, Movement: 0 = 8.46, 24 = 3.54, 48 = 4.23, 72 = 2.27; with a p <0.000. Monitoring in blood pressure, heart rate, respiratory rate, partial oxygen saturation without significant changes and no side effects were recorded.

Conclusions: The patients in the case series with severe pain intensity who received FT 25µg/h decreased significantly in the 72-hour follow-up.

Keywords: Fentanyl; Severe pain; Pain relief; Side effects

Abbreviations: FT: Transdermal Fentanyl; ENA: Analog Numerical Scale; µg/h: micrograms per hour

Introduction

Acute pain is an inevitable experience of life and plays a fundamental role in protecting the host against a large number of threats [1,2]. The presence of pain carries medical, social, and economic problems [3]. The study by Whelan et al reported that 59% of patients who suffered pain during hospitalization, 12% were mild, 19% moderate, and 28% severe [4]. Buvanendran reported that postoperative pain interferes with daily activities in the weeks after hospital discharge [5] Hospitalized pain patients should be evaluated and cared for. To assess pain, the use of one-dimensional scales such as the Visual Analog Scale (VAS), Analog Numerical Scale (ENA) or the Verbal Scale [6,7] is recommended. ENA, introduced into the clinic by Downie in 1978, is important in evaluating treatments [8]. The reduction in pain intensity from 10/10 to 6/10 is a percentage reduction of 33%, which is considered a favorable result [9]. There is a significant correlation (r = correlation) between the Visual Analog Scale and the Analog Numeric Scale, estimated at r = 0.94 [10]. The management of mild - moderate pain includes non-opioid drugs, in cases of

severe pain opioids are the choice, and for safety it should not exceed 30 days [11]. The use of opioids should be individualized, multimodal, considering the diagnosis, severity of pain, functional capacity, and physical limitations of the patient, with the prospect of minimizing side effects with short-acting, low-dose regimens [12]. Fentanyl is a powerful opioid and can be administered through different routes: intravenous, intramuscular, intranasal, buccal and transdermal; This last one has a molecular weight of 337 Daltons, which allows it to easily pass through the skin. The FT is alkali which allows to penetrate easily the keratin stratum corneum [13]. Transdermal patch systems store the medication in a reservoir (medicine dissolved in a liquid-based reservoir or matrix gel). The starting point for evaluating the kinetics of drug release from a transdermal patch is by estimating the maximum value of the compound from the drug flow through the skin flow (J) that is typically expressed in units μg/cm^2/h. The delayed effects of transdermal fentanyl have been estimated between 12 to 16 hours, the conversion of transdermal fentanyl to intravenous route can be achieved in a 1: 1 conversion being safe and effective [14,15]. Clinical studies of FT in hospitalized patients have been in moderate to severe pain due to various pathologies. Samala et al evaluated FT in 17 cancer patients, who were simultaneously placed on the FT patch and a continuous intravenous infusion for 6 hours of fentanyl (transposition time = time of onset of action of the FT patch), with follow-up of 24 hours, resulting in continuous improvement of pain between 6 and 24 hours [16]. Kim et al, in 22 hematologic patients with mucositis and pain from chemotherapy; 19 of these received FT 25μg / h, 6 of the 19 required an escalated dose of FT 50μg / h and the intensity of pain with the visual analog scale (EVA) before treatment and subsequent evaluation on days 2, 6 and 10 corresponded to: EVA = 6.68, 5.17, 3.42 and 2.13 with a p 0.001; sleep improvement was in 8 (42.1%) and mood improvement in 7 (36.8%). In 3 (13.63) patients, FT was withdrawn due to severe side effects: dizziness, vomiting, generalized skin rash [17]. The FT 25μg/h in acute postoperative pain due to laparoscopic cholecystectomy, applied 14 hours before surgery against intravenous infusion of fentanyl of 25μg/h, measured and compared the analgesic concentrations at admission and at 1, 6, 12, 24, 48 hours, pain score, analgesic rescue and respiratory depression. In the FT the maximum concentration (3.27±0.34ng/ml) was 1 hour after the operation, in the intravenous group the maximum concentration (2.9±0.42ng/ml) 24 hours postoperatively. Pain scores, analgesic rescues without significant differences between the 2 groups, no case of respiratory depression occurred [18]. The FT 50μg/h in the relief of postoperative pain at 24 hours in third molar extraction surgery was compared with diclofenac, in the intensity of postoperative pain, consumption of postoperative analgesics, and it was found that they were significantly lower with FT p <0.05; and the duration of analgesia was longer with FT; p <0.05 [19]. FT 50μg/h applied 10 to 12 hours prior to total knee arthroplasty compared to placebo patch for postoperative pain with 48-hour follow-up, it was found that with FT there was less consumption of morphine at 24 and 48 hours compared to placebo which respectively were: 15.40±12.65 and 24.90±20.11mg versus 33.60±19.06 and 57.80±12.65mg; p<0.001. Pain intensity with ENA at rest and movement in 48 hours was lower with FT. Ambulation, nausea, vomiting score was higher for FT without significant statistical differences. Sedation was minimal in both groups and without significant statistical difference, no case of severe respiratory depression [20]. The presence of side effects of FT in its iontophoretic form (40μg/activation) in 90 patients with spinal surgery compared to 80 patients with patient-controlled analgesia (PCA) with morphine (1mg/dose) in postoperative pain, reported that the percentage of secondary events in general for FT was 74.4% versus 77.5% for morphine with PCA (p=.318). The most common side effects for iontophoretic FT versus Morphine PCA corresponded respectively: nausea 37.8% vs 47.5% p (= .217), vomiting 17.8% versus 15.0% (p = .682), headache 13.3 versus 7.5% (p = .318). The estimate of specific side effect rates for each opioid was similar between groups (iontophoretic FT 54.4% versus 63.8% Morphine PCA, p=.275). The significant differences between the 2 groups were: erythema at the application site, being 27.8% for iontophoretic FT versus 0% for Morphine PCA with a statistically significant difference (p <.0001); application site itching for iontophoretic FT 6.7% versus 0% Morphine PCA (p = .030), reactions were considered mild to moderate and resolved spontaneously [21]. The use of opioids induces intestinal dysfunction, constipation is frequent, the pathophysiology is multifactorial. Intestinal dysfunction should be evaluated in all patients receiving opioids, the Rome IV criteria are a good identification instrument [22].

Material and Methods

Retrospective case series that included the records of patients with severe acute pain who received multimodal analgesic management, without satisfactory pain relief, which led to the use of Fentanyl Transdermal 25μg/h. Study carried out at the Specialty Hospital XXI Century National Medical Center from March - July 2019. Inclusion criteria: records of patients with nociceptive/neuropathic pain, severe ENA≥7 with analgesic management for 24 hours and without sufficient analgesic response (≥30%), who received a FT 25μg/h patch lasting 72 hours, which in the same time that the FT was applied, continuous intravenous infusion of fentanyl was started 300 micrograms for 12 hours (ratio patch FT / IV infusion 1:1), over 18 years, male or female, complete clinical record. Elimination criteria: patient records with incomplete information, patients with FT without concomitant infusion of intravenous fentanyl, undergoing emergency surgery, undergoing mechanical ventilation, transferred to intensive care. The sample size calculation was convenient. The collection of information was initiated after approval and authorization of the study by the Institutional Bioethics and Research Committee, Folio R-2019-3601-254. A data collection sheet was used that included the study variables that were transferred to a database in a Microsoft Excel sheet. Analysis of results with the statistical program SPSS version

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19. The selected cases of the study included sociodemographic variables, pain intensity with the one-dimensional instrument Analog Numerical Scale (ENA) evaluated at 0, 24, 48, 72 h, average pain intensity in rest and movement. Descriptive statistics were applied, Student's t-test for related samples considering statistically significant p <0.05.

Operational description of the study

With the approval of the study by the corresponding committees, the information was collected in the period of March - July 2019, from the patients who received FT 25μg/h and simultaneously intravenous infusion of fentanyl 300μg for 12 hours. The information was obtained with the use of a data sheet containing the variables of interest. The capture of the information was always carried out by the same associate researcher, after training. The generated sheets were delivered to another researcher who emptied the data into an encoded Excel sheet. The information was processed by a statistician certified in the SPSS statistical package version 19.

Results

Case series that included 13 patients, the demographic characteristics (table 1) were: 5 (38.5%) women/8 (61.5%) men, average age 57 years (range 26 - 78 years), average height 1.59 meters, weight average 68.46 kilograms. Patients with Body Mass Index ≥ 30, 8 (61.5%); smokers 6 (61.6%); High School was the most common school level with 4 (30.8%). The Physical State of the Patient (ASA) III was 9 (69.3%). The pathologies were: Postoperative pain: 5 (38.5%); 1 Fournier syndrome, 1 post-operative exploratory laparotomy with chronic kidney disease, 1 post-operative thoracotomy with endopleural catheter placement, 1 post-operative right lung abscess drainage and endopleural catheter placement, 1 amputee at the supracondylar lower limb level with diabetic neuropathy, chronic kidney disease, and upper GI bleeding. Bone pathology: 4 (30.8%) patients; 1 pathological vertebral body fracture T6, 1 spondylodiscitis and cervical lysis, 1 vertebral osteomyelitis L2-L3 with soft tissue extension, 1 displaced rib fractures. Arterial pathology: 3 (23.1%) patients; 1 acute aortic syndrome, 2 acute lower limb Rutherford III arterial insufficiency. The multimodal analgesic management of the patients prior to the placement of the FT patch and intravenous infusion of fentanyl (300μg for 12 hours) was: intravenous buprenorphine 8 (61.6%), intravenous tramadol 5 (38.5%). All patients received non-steroidal anti-inflammatory pain relievers, paracetamol, gabapentinoids. Those 13 patients who received the FT continued with the same doses of non-steroidal anti-inflammatory painkillers, paracetamol, gabapentinoids. The results in the evolution of pain intensity (Graph 1) were measured with the ENA, in the average both rest and movement, at times 0 = basal (after placement of FT), 24, 48, 72 h. The results in pain relief with the average ENA at the different times were: 0 = 8, 24 = 2, 48 = 3, 72 = 2 (p <0.000). The results of pain intensity with ENA at rest (ENA: R) and movement (ENA: M) at times 0, 24, 48, 72 h (Graph 2) showed a statistically significant difference (p <0.000). The differences in the results of pain intensity (ENA) at times 0, 24, 48, 72h, in the average, rest and movement and statistical differences (table 2). Side effects from FT in patients were not presented, 4 patients (30.7%) already suffered from chronic constipation, in addition, antiemetics, intravenous fentanyl were previously used, and FT were low and short-term.

Table 1: Demographic characteristics of 13 patients who received transdermal fentanyl.

Characteristics	(%)
Gender	
Men	8 (61.5)
Women	5 (38.5)
Average age years [range]	57 [26 – 78]
Average size	1.59 m
Average weight	68.46 kg
IMC (kg/m^2)	
20-24.9	5 (38.5)
25-29.9	5 (38.5)
>30	3 (23.1)
Smoking	8 (61.5)
Scholarship	
Primary school	3 (23.1)
Middle school	4 (30.8)
High School	2 (15.4)
Bachelor's Degree	3 (23.1)
Master's Degree	1 (7.7)
ASA	II:1 (7.7) /III:9 (69.3) /IV:3 (23.1)
Pathology	
Postoperative	5 (38.5)
Bone pathology	4 (30.8)
Arterial pathology	3 (23.0)
Lyme's desease	1 (7.7)

(%): percentage; m: meter; Kg: kilogram; BMI: body mass index expressed in kg/m^2; ASA: Physical State of the Patient

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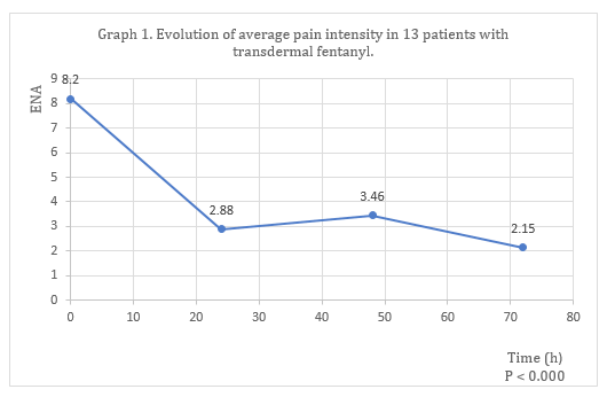
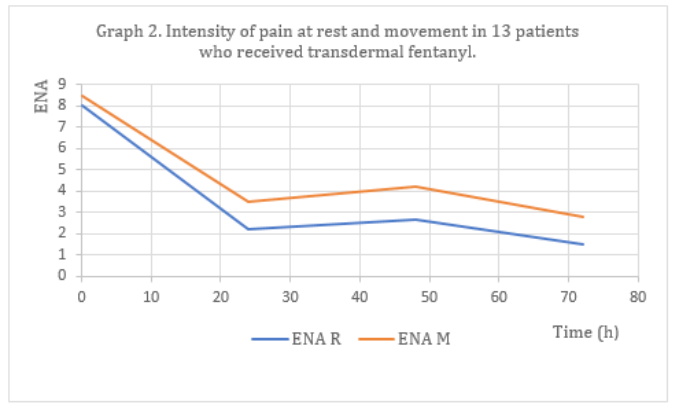
Table 2: Main differences in ENA pain intensity in 13 patients who received transdermal fentanyl.

Time h	ENA (DE±)	Average Difference	p
Average Pain Intensity			
0 - 24	8.23 (.85) - 2.28 (1.87)	5.95	0
0 - 48	8.23 (.85) – 3.46 (1.66)	4.77	0
0 - 72	8.23 (.85) – 2.15 (1.60)	6.08	0
Pain Intensity at Rest			
0 - 24	8.0 (1.08) – 2.23 (2.00)	5.77	0
0 - 48	8.0 (1.08) – 2.69 (1.7)	5.31	0
0 - 72	8.0 (1.08) – 1.54 (1.76)	6.46	0
Intensity of Pain in Movement			
0 - 24	8.46 (.77) – 3.54 (1.93)	4.92	0
0 - 48	8.46 (.77) – 4.23 (1.78)	4.23	0
0 - 72	8.46 (.77) – 2.77 (1.65)		0

ENA: Analog Numerical Scale; R: Rest, M: Movement; P: Average; SD: Standard Deviation; P: Value P



Graph 1: ENA: Analogue numerical scale; h: Hours.



Graph 2: ENA: Analog numerical scale.
ENA: R: Analog Numerical Scale at Rest; ENA: M: Analog Numerical Scale in Motion; h: Hours.

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Discussion

The 13 hospitalized patients reported had various pathologies with a common characteristic that was severe pain (ENA = 8), and that they did not present pain relief with multimodal analgesic management, in such circumstances the use of powerful opioids is justified [11], and these should be planned individually to reduce the presence of side effects, with short-term and low-dose regimens [12], such recommendations were applied in this series of cases. The use of FT is indicated in severe acute pain as it is a powerful opioid that easily crosses the skin barrier [13]. Reports in clinical practice of FT in patients with acute pain is with the parallel administration of continuous intravenous fentanyl in a 1: 1 ratio for 12 to 16 hours due to the delay in the initiation of action (transposition period) of the FT patch. which is the time in which it reaches the analgesic serum levels, in the patients of this series this recommendation was carried out since after the application of 1 patch of FT 25μg/h, they simultaneously received the infusion of intravenous fentanyl 300 μg to 12 hours [14,15]. FT has been used successfully in various studies of acute postoperative pain, in laparoscopic cholecystectomy [18] applied 14 hours before surgery, obtaining good results in the relief of postoperative pain, at the times respectively: 1, 6, 24, 48h with the ENA = 5, 2.8, 1.6, 1.0. The management of postoperative pain in molar extraction surgery with FT (50μg/h) for the first 24 hours compared to diclofenac was favorable in the reduction of pain intensity (evaluated with the visual analogue scale), lower consumption of analgesics with $p < 0.05$, longer duration of analgesia with FT versus diclofenac, with $p < 0.05$ [19]. The FT 50μg/h applied between 10-12 hours prior was studied in postoperative pain for knee toral arthroplasty compared with placebo patch at 48-hour follow-up. The results in morphine consumption at 24 and 48 hours with FT versus placebo corresponded respectively to: 15.40±12.65 and 24.90±20.11mg versus 33.60±19.06 and 57.80±12.65mg, p≤0.001; pain intensity with ENA at rest and movement at 24 hours, for FT ENA rest = 2.73±1.95, movement = 4.39±2.37; placebo ENA rest = 4.64±1.60, movement = 6.42±1.40, p 0.002 (20). Our results are very similar in pain intensity, with $p<0.000$ representing a statistically significant difference. In pathology of the spine related to compressive fractures due to osteoporosis, the FT 12.5μg / h was compared with vertebro percutaneous plasty, in the intensity of pain in the short and long term, in the short term at 3 weeks, the intensity of pain with the scale. analog visual; with the FT it was 5.6 and 6.1 with the vertebro plasty, p=0.355, at 4 weeks differences were observed, being for the FT 5.8 and 3.4 vertebro plasty, p=0.022 [23], the cases of the series that we present corresponding to bone pathology benefited from pain relief with FT. Pain caused by critical limb ischemia is challenging since analgesic therapies are not effective, the best treatment is based on disease modification and is usually with revascularization that improves reperfusion [24]. Critical limb ischemia produces pain that is difficult to control, pain relievers such as acetaminophen, nonsteroidal anti-inflammatory pain relievers, gabapentin, lidocaine, and ketamine help, but have not been shown to be very effective, requiring the use of epidural blockade and strong opioids [25.26]. The patients in this series received the analgesics described and the relief was minimal, therefore the need for the use of FT.

Lyme disease can trigger pain [27], the recommended pain relievers are gabapentin, pregabalin, amitriptyline, paracetamol, tramadol, however these do not have strong evidence, and strong opioids are not recommended for their adverse effects [28,29]. In a report of 4 cases with Lyme disease and severe pain, in 2 patients the use of morphine, meperidine, hydromorphone in the short term for pain control was warranted [30]. In some health systems tramadol and oxycodone are considered a second option in the treatment of pain related to Lyme disease [31], in Australia the use of FT has been used in patients with pain with a history of use and non-use of opioids , indicated in diseases of the central nervous system, circulatory, respiratory, gastrointestinal, the musculoskeletal system and connective tissue, genitourinary system and in terminal kidney disease; and found that the risk of opioid overdose was high in the first week after starting the opioid [32]. The patient with Lyme disease pain in our series had previously received opioid, and FT rotation benefited from pain relief. The main side effects with FT in various doses (50, 75, 100, 125μg/h) for the control of acute pain in abdominal, orthopedic, lumbar fusion, thoracotomy surgery, applied 2 hours before surgery in 5 open studies (2 FT studies in which it was replaced at 24 hours, and in 3 at 72 hours), in all studies patients received intraoperative fentanyl as well as supplemental analgesia with morphine or meperidine, in which an incidence was reported of nausea 36%, vomiting 18% that corresponded to patients with FT replacement at 24 hours; in patients who did not replace the FT patch and remained for 72 hours, they had no side effects. In 6 controlled studies comparing FT (50, 75, 100μg/h) with placebo in abdominal / orthopedic surgery, at the times of postoperative pain assessment at 24, 36 and 72 hours, respiratory depression was reported in 20 of 98 cases. , 4 merited the use of naloxone. 2 patients opioid reduction and use of oxygen mask, 3 removal of FT, 1 use of oxygen mask, 1 patient who was awakened. In this regard, in open and controlled studies, it was identified that supplemental analgesia was elevated in the first 24 h, this reflects the prolonged time of between 14 and 24 hours of onset of TF action [33]. In a double-blind controlled clinical trial in 42 patients undergoing shoulder surgery compared FT 75μg/h against placebo in the treatment of postoperative pain in the first 24 hours, the side effects between FT / Placebo were: nausea: 77% / 60 %, vomiting: 73% / 30% (p .014), urinary retention: 27% / 10%, itching: FT 14% / 20%, dizziness: 4% / 10%, headache: 4% / 5% [34]. in the case series that we presented, no patient reported side effects, perhaps because the analgesic doses used of intravenous fentanyl, as well as the FT patch were low, that the patients had already received opioids, the use of antiemetics; when starting with intravenous fentanyl, rescues were avoided in the first 24 hours and afterwards, thus avoiding overdose and therefore side effects. This retrospective case series has limitations such as bias in the quality of obtaining information and therefore in the results.

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Currently the FT patch in postoperative pain is not an indication since it is not approved by the regulatory health agencies, in this regard various studies confirm its use. The clinical results we obtained on analgesia are consistent with previous reports, and differences in the presence of side effects are likely when using a low dose of the FT patch, and not using additional doses of opioid.

Conclusions

Patients in this severe pain case series who received the 25µg/h FT patch had satisfactory pain relief for 72 hours. In hospitalized patients with severe pain, FT is an option to consider, always taking into account the following recommendations [35]: The American Society of Anesthesiology has not currently included in the guidelines for the practice of perioperative management of FT, although studies are being carried out on postoperative pain. Avoid body and skin warming since cutaneous blood flow is increased, a body temperature of 40 degrees Celsius increases the absorption rate by one third, actions that increase the temperature of the patient for 10 hours increases the plasma levels of the patch of FT at 120 to 184%, this has led to consider that policies are oriented not to use FT patches as a standard in the perioperative period. Plasma levels after FT removal persist for 24 hours. FT is contraindicated in patients: under 12 years of age, weighing less than 50kg, with edema, erythema, papules, pruritus, severe lung disease, hypoxia, hypercapnia, respiratory and cachectic depression.

Interest Conflict

The authors who participate in this article declare that we are without conflict and free of interest.

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