REVIEW ARTICLE

The Efficacy of Fentanyl for Pain Management in Emergency Department: Review Article

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Fentanyl is a strong opioid and it is widely used for pain relief. In this review, we evaluated the efficacy of fentanyl in pain management in the emergency department. For this review, we searched scientific search engines including google, google scholar, Cochrane library, Medline, and PubMed and collected original articles, including randomized controlled trials, comparative studies, cohort and case series related to fentanyl and its administration in the emergency department from 2010 to 2016. In this review, 8 articles and 44493 patients were evaluated. Four articles were retrospective and 4 articles were prospective of these four articles were randomized placebo controlled and double blinded. Among eight articles, six of them compared the efficacy and adverse events of fentanyl with other opioids. We found fentanyl significantly decreases pain intensity in patient with acute pain in the emergency department. Moreover, it is more effective than morphine and methoxyflurane.

keywords: **acute pain, analgesia, fentanyl, pain management, emergency department**

Pain is the most prevalent complaint among patients referring to the emergency department [1]. The previous reports revealed pain is chief complaint among 75 % of patients and it is more weakening than cancer and heart diseases [1-3]. Untreated pain may elevate the level of plasma catecholamine, glucose, antidiuretic hormone, cortisol, and acute phase protein [1-3]. To overcome these acute phase reactants, a diverse class of drugs and methods such as opioids, benzodiazepines, and local anesthesia are used to ameliorate the level of pain and distress [4-5]. Opioids such as meperidine, morphine, hydromorphone, fentanyl, and methadone are the most common agents used for pain relief in the emergency department (ED) [6]. Among these drugs, the most appropriate agent regarding BMI, age, and intensity of pain should be chosen as an analgesic or sedative. Fentanyl is a highly lipophilic, μ-opioid receptor agonist and diffuse across blood-brain barrier rapidly [7]. Its equilibration t ½ is about six minutes and fentanyl are 100-fold more potent than morphine [8]. Fentanyl metabolized in the liver [9-11] and may induce some important and life-threatening adverse effects such as hypoventilation and respiratory depression, but, they are rare. In general, like as other opioids, nausea, vomiting, pruritus, and urinary retention are the commonest adverse effect of fentanyl [12-13]. The routes of administration of fentanyl include transdermal, intravenous, subcutaneous, oral transmucosal, sublingual, and neuraxial. Moreover, several formulations are accessible [14]. Previous practices have reported that fentanyl is well tolerated without any serious adverse effect [15-16]. Moreover, it effectively decreases the level of pain as much as other analgesics with a lower serious side effect [17]. In this review, we evaluated the effectiveness and possible side effects of fentanyl for pain relief in adult patients referring to the emergency department with acute pain.

Data collection

To data collecting for this review, we searched google, google scholar, Cochrane library, Medline, and PubMed and collected original articles, including randomized controlled trials, comparative studies, cohort, and case series related to fentanyl and its administration in the emergency department from 2010 to 2016. The following keywords were used: fentanyl; emergency department and pain management. The search was further limited by age group to adults, moreover, the duration of pain and the articles evaluating patients with chronic pain were excluded. Moreover, articles with duplicated records and irrelevant full text were excluded. Finally, 8 articles met the inclusion criteria and were enrolled to this review including one cohort and seven comparative studies including three double blinded placebo controlled trials.

Results

In this review, 8 articles that were conducted between 2010 to 2016 were recruited and totally 44493 patients were evaluated. Four articles were retrospective and 4 articles were prospective. The later four articles were randomized placebo controlled and double blinded. Among all eight relevant articles, six of them compared the efficacy and adverse events of fentanyl with other opioids such as morphine and methoxyflurane and two of them compared the pain severity before and after fentanyl prescription. The route of administration of fentanyl in most of the

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experiences was intranasal but it was intravenous for morphine. The most of the articles demonstrated that fentanyl decreases pain score after administration and is more potent than morphine and methoxyflurane with lower side effects. The characteristics of the trial are summarized in (Table 1). Moreover, table 2 shows the number of the participants in each trials, the dose of administered drugs,the level of pain reduction etiology of pain and possible adverse effect of treatments (Table2).

Table 1- the characteristics of the trials

Authors	Year	Setting	Route of administration	Type of study
Middleton et al	2010	No blinding, no randomization(N=42,844)	IN fentanyl vs IV morphine vs methoxyflurane	Retrospective, comparative, observational
Taylor et al	2010	randomized, placebo-controlled, double-blind(n=114)	Fentanyl pectin nasal spray (FPNS)	Prospective randomized
Fleischman	2010	No blinding no randomization(n=718)	IV Fentanyl Vs Morphine	Retrospective, comparative
Johnston et al	2011	No blinding no randomization(n=1024)	IN fentanyl vs methoxyflurane	Retrospective, comparative, observational
Wedmore et al.	2012	No control, no randomization, no blinding(N=197)	oral transmucosal fentanyl citrate (OTFC) Fentanyl (different doses)	prospective Cohort
Wenderoth et al.	2013	No control, no randomization, no blinding(N=168)	IV Fentanyl vs morphine	Retrospective comparative
Farahmand	2014	placebo-controlled, double-blind randomized clinical trial. (N=90)	Nebulized fentanyl vs intravenous morphine	controlled trial
Deaton	2015	randomized, double-blinded, double-placebo–controlled trial(N=40)	Nebulized fentanyl vs intravenous morphine	controlled trial

Table 2- The number of the participants, dose, level and etiology of pain and possible adverse effects

			NRS (1-10)		
Author (Year)	Number of Patients	Dose of analgesic	Pain score at admission→ after treatment	etiology of pain	Side effects
Middleton et al. (2010)	42844 patients; Morphine (12955), Fentanyl (3778), Methoxyflurane (19235), Combination (morphine, fentanyl or methoxyflurane) (6876).	Morphine 0.5 mg/kg IN fentanyl 90 µ g	8.4→3.9	Pain in Abdomen, back, respiratory, chest, obstetrics	Not reported
Taylor et al. (2010)	114 (FPNS and placebo)	BTCP: 7 episodes for case and 3 for placebo	Two point discretion in pain intensity	cancer	Patients with adverse events were excluded
Fleischman (2010)	718 (355 morphine, 363 fentanyl)	Morphine IV 2--5 mg, maximum 20 mg. Fentanyl 50-µg IV dose, maximum 200 µg.	morphine (8.3→5.4), fentanyl (8.1→5)	Extremity and hip pain, burns Atraumatic abdominal and pelvic pain ischemic chest pain, Back pain , Other chest pain , Head and neck pain	Nausea, Hypotension

Table 2- The number of the participants, dose, level and etiology of pain and possible adverse effects (Continued)

			NRS (1-10)		
Johnston et al. (2011)	1024; MTX (465), INF (393), both (162)	INF (15-180 µ g first,15-60 µ g second dose), MTX (3 ml at a concentration of 0.2% - 0.4%)	MTX (8→5.5), INF (7.6→4.4), both (8.8→5.4)	visceral pain(abdominal,cardiac,renal)	Not report
Wedmore et al. (2010)	197 (156 received OTFC)	OTFC (962.4 (452.7) µ g	8→ 3.2	Gun shot, orthopedic injuries, laceration	nausea, pruritus, drowsiness, dizziness
Wenderoth et al. (2013)	168 (84 in fentanyl and 84 in morphine group)	morphine 4 mg IV, fentanyl 50 µ g IV.	fentanyl= 10→8, morphine= 8→6	All types of trauma	In fentanyl: hypotension, respiratory depression, oxygen desaturation
Farahmand et al. (2014)	90 patients (47 nebulized fentanyl ,43 morphine)	nebulized fentanyl (4 µg/kg) and IV normal saline as placebo. IV morphine (0.1 mg/kg) and nebulized normal saline as placebo	fentanyl (8.7→3.5), morphine (8.4→3.8)	Wound and soft tissue injuries Fractures Sprains and strains	Nausea, vomiting Lightheadedness, loss of consciousness
Deaton,et al. (2015)	40(20 NF,20 IVM)	IVM= 0.1 mg/kg 5, NF= 2 µg/kg	IVM=7.5, →5.9 NF=6.6→2.8	undifferentiated abdominal pain	Not reported

IN=intranasal,IVM= intravenous morphine,NF= nebulized fentanyl , OTFC= oral transmucosal fentanyl citrate , MTX)=Methoxyflurane ,INF: intranasal Fentanyl , Fentanyl pectin nasal spray(FPNS), breakthrough cancer pain =BTCP

Discussion

The management of pain is a wide field and several hypotheses about the pain relief and agents that can decrease the pain are presented, but most of these guidelines and recommendations are insufficient. For instance, several opioid agonist-antagonists such as buprenorphine, butorphanol, nalbuphine, and pentazocine have been used for decades to reduce pain in patients with acute pain in the emergency department, in the ambulance or in the hospital with some useful effect but with serious complications such as dysphoria [18]. In this review, we gathered the articles that were performed to evaluate the efficacy of fentanyl on pain relief in patients in the emergency department. Four studies have compared the efficacy and adverse events of fentanyl with morphine, two of these were double blinded randomized trials including; A study by Deaton et al in 2015 that compared the effect of nebulized fentanyl (NF) (2 µg/kg) with intravenous morphine (IVM) (0.1 mg/kg) in patients with acute abdominal pain presenting to emergency departments. They revealed that the pain reduction occurred sooner in the NF group and more sustained. Moreover, the authors showed that the satisfaction of patients and doctors in fentanyl group was more than morphine group [18]. Another study by Farahmand in 2014 also compared the effectiveness of nebulized fentanyl (4 µg/kg) (47 patients) with intravenous (IV) morphine (0.1 mg/kg) (43 patients) and showed no difference regarding pain reduction and patients' satisfaction between two groups after 10 minutes, however, after 15 the pain relief in fentanyl group was significantly more than morphine [19]. Moreover, one non-blinded study by Wenderoth et al.in 2013 compared the analgesic response and safety of intravenous morphine with fentanyl on adult trauma patients who referred to the emergency department (ED). The pain score reduction in two groups did not differ significantly, although the pain reduction in fentanyl occurred sooner than morphine group. The difference between two groups regarding side effects was not significant [20]. Another non-blinded study by Fleischman in 2010 was conducted on 168 patients who were assigned in fentanyl (N=84) and morphine (N=84) groups. The severity of injury in fentanyl was more than morphine group. Five patients in two groups regularly used opioids before admission.

They found that morphine and fentanyl provide the comparative analgesic effect, however, the opioids consumption in fentanyl groups was higher than patients receiving morphine. On the other hand, the adverse events in morphine group was more than fentanyl group [21]. Among the comparative surveys, one non-blinded study by Johnston et al. compared the pain relief effect of intranasal fentanyl with methoxyflurane and proved that fentanyl was more effective than methoxyflurane [22]. Only one study among surveys evaluated in this review by Middleton compared two analgesics including morphine and methoxyflurane with fentanyl and demonstrated that IV morphine and intranasal fentanyl was more effective than methoxyflurane regarding the pain relief among the out patients. Moreover, in comparison between fentanyl and morphine, they proved that morphine was more effective than fentanyl. While IN

fentanyl was more accessible and useable [23]. Only one of the study was double-blinded controlled trial and compared the efficacy of fentanyl with controls conducted by Taylor et al that confirmed fentanyl pectin nasal spray (FPNS) was an effective agent in pain relief. Additionally, they indicated that FPNS is well tolerated and leads to more patients' satisfaction [24]. Three of practices were conducted by the authors as cohort study and compared the pain score before and after fentanyl administration. Wedmore et al. in 2012 studied the effectiveness and safety of 286 out hospital patients that were treated with oral transmucosal fentanyl citrate (OTFC) and revealed a significant difference between pain score before and 15 ,30 minutes after treatment. Moreover, they emphasized that fentanyl is safe, however, in high dose administration, nausea, hypoventilation and O2 saturation less than 90% may occur [25].

Limitations of review: Of the 8 studies included in this review, only three studies were randomized and double-blinded, which emphasizes the fact that further high quality double-blinded randomized controlled trials are required to validate results reported in these articles. Moreover, we did not enroll studies on children and all recruited practices were conducted in patients more than 16 years of age. Studies in children may lead to different results. Additionally, we could not confirm that whether fentanyl is a useful agent in the patients with chronic pain such as patients with cancers other painful chronic diseases

Conclusion

In summary, the studies proved that fentanyl significantly decreases the acute pain intensity and well tolerated by the patients. The adverse effects related to fentanyl were not serious and were transient. Pain reduction is related to function improvement in patients and increased the level of patients' satisfaction. A review by Downey et al indicated that pain reduction increases satisfaction and function of patients, moreover they emphasized that pain relief improves patients doctor communication [26]. The most of the experiences reviewed in this article used fentanyl as an intranasal spray and showed this is an alternative to the traditional routes of administration such as oral administration and intravenous injection. Finally, we concluded that fentanyl significantly decreases the pain intensity in patients referring with acute pain to the emergency department. Moreover, it is more effective than morphine and methoxyflurane in the most of the patients.

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