Review Article

Nebulized Fentanyl in Acute Pain: A Systematic Review

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Abstract

Objective: To provide a systematic review of the current role of nebulized fentanyl in acute pain and potentially other conditions. Data Sources: A MEDLINE literature search inclusive of the dates 1946 to May 2016 was performed using the following search terms: fentanyl and administration, inhaled. Excerpta Medica was searched from 1980 to May 2016 using the following search terms: exp fentanyl/inhalation drug administration. Additionally, Web of Science was searched using the terms fentanyl and pain inclusive of 1945 to May 2016. Study Selection and Data Extraction: We utilized the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines to select English language, human primary literature, review articles, and supporting data assessing the efficacy of nebulized fentanyl in acute pain. Data Synthesis: Seven clinical trials have demonstrated no difference in efficacy between nebulized fentanyl and intravenous (IV) opioids. Few adverse effects were reported; however, the trials were of short duration. Nebulized fentanyl appeared to be a rapid-acting analgesic that does not require IV access. Conclusion: Evidence suggests that nebulized fentanyl is as effective as IV opioids in the treatment of acute pain, with relatively few adverse effects. However, questions remain about the extemporaneous preparation of fentanyl nebulized solution, the variability in nebulization devices, and ensuring consistent drug delivery to distal airways in the clinical setting. The abuse potential of nebulized fentanyl should also be considered.

Keywords

pain management, analgesia, emergency medicine, dosage forms, pharmacokinetics

Introduction

Patients seeking acute pain relief account for as much as 70% of emergency room visits.¹ Although emergency room clinicians manage patients with pain on a frequent basis, inconsistencies and inadequate pain relief in patients is common.² The relief of pain is one of the fundamental therapeutic goals of patient care. For centuries, opioid analgesics have been the foundation of pharmacotherapy for relief of pain, with intravenous (IV) opioids providing the most rapid pain relief.³ However, IV drug administration requires placing an IV catheter, often causing distress to the patient. In addition, the rate of unsuccessful catheter placement can be as high as 12% to 26%. This has resulted in the search for alternative methods of rapid drug administration that does not require the placement of an IV catheter.⁴,⁵

Fentanyl is a synthetic opioid derivative, which is a potent agonist at the μ-opioid receptor.⁵ It is widely used in anesthesia and for acute and chronic pain management⁶,⁷ and has a rapid onset and relatively short duration of action. It is primarily given by the IV route but can be given transdermally, sublingually, intranasally, intrathecally, and by inhalation.⁸ Intranasal fentanyl has been studied as a noninvasive method of fentanyl administration for quick pain relief. Fentanyl is rapidly absorbed by this route and reaches maximum plasma levels in about 2 minutes. It is usually prepared using the IV preparation (50 µg/mL) in a small syringe with a nasal atomizer device attached to the syringe. The solution is then absorbed across the nasal mucosa directly into the central nervous system, bypassing first-pass metabolism. This is in contrast to nebulized fentanyl, which is delivered into the lungs and absorbed through the pulmonary circulation. Fentanyl given intranasally has been shown to be an effective analgesic for acute relief of pain in a number of controlled trials.¹⁰⁻¹⁴ An extensive Cochrane review of intranasal fentanyl found that it was effective in children with acute moderate to severe pain. This review concluded that intranasal fentanyl caused few adverse effects but that it should not be used in children younger than 3 years old because these children have difficulty with efficiently using the nebulizer device. The maximum

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volume of fluid that can be administered intranasally limits the dose of fentanyl that can be administered, sometimes resulting in repeating doses of fentanyl to achieve a therapeutic end point. Using the standard 50-µg/mL IV concentration can result in a large volume of fluid given intranasally with resultant dripping, swallowing, and sneezing causing loss of drug.11

Nebulized fentanyl has been investigated as a promising, noninvasive, alternative method of fentanyl administration for acute pain.4,15-18 The purpose of this article is to review the use of nebulized fentanyl in the treatment of acute pain, and other possible indications, using a systematic methodology.

**Literature Search**

To provide systematic and transparent reporting, we incorporated the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.17 Our literature search consisted of MEDLINE (1966 to May 2016) searching the Medical Subject Headings (MeSH) terms fentanyl and administration, inhaled. Web of Science (1945 to May 2016) was also searched using the search terms fentanyl and pain. Excerpta Medica (1980 to May 2016) was searched using EMBASE with the key terms exp fentanyl/inhalation drug administration and pain. Only English-language articles were considered in our literature evaluation. Bibliographies of all relevant articles were reviewed for additional citations. See Figure 1 for inclusion and exclusion criteria.

**Fentanyl and Morphine Pharmacokinetics After Inhalation**

**Early Anesthesiology Literature**

Fentanyl was first introduced into clinical practice in the 1960s.19 It was originally used almost exclusively as a single IV dose. The distribution half-life (t½ α) of fentanyl is very...
short (1.0-1.7 minutes). Fentanyl quickly distributes from the vascular compartment to fat and muscle compartments and crosses the blood-brain barrier by diffusion and active transport.\textsuperscript{19} The elimination half-life ($t_{1/2}$) is highly variable, ranging from as low as 3.1 hours to 7.9 hours and can be up to 15 hours in geriatric patients.\textsuperscript{9,19} The elimination half-life increases with continuous infusion of fentanyl as a result of saturation of muscle and fat compartments. Volume of distribution for fentanyl ranges from 3.2 to 5.9 L/kg, whereas protein binding (at pH 7.4) is about 84%.\textsuperscript{9,19} Fentanyl also has extensive first-pass sequestration in the pulmonary vascular, which can delay onset to analgesia.\textsuperscript{20,21}

Mather et al\textsuperscript{23} evaluated the absorption of fentanyl from the pulmonary vascular, which can delay onset to analgesia.\textsuperscript{20,21} It is metabolized by the cytochrome P-450 (CYP 3A4) system to norfentanyl, hydroxypropionyl fentanyl, and hydroxypropionyl norfentanyl; none of these metabolites are pharmacologically active.\textsuperscript{22}

Worsley et al\textsuperscript{8} were the first to characterize the absorption of fentanyl by the inhalation route. Six patients were given 100 µg of fentanyl by inhalation, and 7 were given 300 µg (see Table 1\textsuperscript{8,23,24,25,26}). They found no peak concentrations after the 100-µg dose, and levels plateaued at around 0.04 ng/mL. Peak concentrations of 0.4 ng/mL were achieved after the 300-µg dose and slowly declined to 0.1 ng/mL after 15 minutes. No significant pharmacokinetic modeling or analysis was performed by these investigators because the primary purpose of the study was to assess clinical pain management.

**Nebulized Fentanyl Pharmacokinetics**

Mather et al\textsuperscript{23} evaluated the absorption of fentanyl from the pulmonary route using an efficient oral inhaler device. They studied 15 healthy volunteers over an 8-week period to characterize the absorption and pharmacokinetics of aerosolized and IV fentanyl. They administered doses of 100 to 300 µg using a SmartMist breath-actuated metered dose inhaler and compared plasma levels with the same dose given intravenously. The drug concentration-time profiles between the 2 different routes of administration were similar with aerosolized fentanyl; however, time to maximum concentration was significantly longer for nebulized fentanyl (4 to 9 minutes) versus IV fentanyl (2 to 4 minutes). Volunteers reported feeling the effects of fentanyl almost immediately after both inhalation and IV administration.

MacLeod et al\textsuperscript{24} examined the pharmacokinetics of nebulized fentanyl in 5 healthy volunteers. In phase 1 of the study, 10 individuals received 25 µg of fentanyl by inhalation and by IV injection in a crossover study design. In phase 2, 40 individuals were split into 4 groups (10 individuals/group), each receiving an increasing dose of nebulized fentanyl (50, 100, 150, and 300 µg). Bioavailability of nebulized fentanyl was calculated to be 96.8% during the phase 1 crossover trial. Although not statistically significant, the time to maximum concentration for nebulized fentanyl was 20.5 s versus 31.5 s for IV fentanyl. The time to maximal concentration for nebulized fentanyl was approximately 50% faster in the study by MacLeod et al when compared with that of Mather et al. This is most likely a result of the different aerosolized device used and its ability to deliver fentanyl to the distal airways, allowing rapid absorption across the alveolar membrane into the systemic circulation. In the phase 2 dose-escalation stage of the trial, serum concentrations following the administration of nebulized fentanyl followed predictable, dose-dependent pharmacokinetics.

Fentanyl has also been evaluated as a liposomal-encapsulated aerosol nebulizer. Hung et al\textsuperscript{27} compared the pharmacokinetics of 200 µg IV fentanyl with 2000 µg of a mixture of free (50%) and liposome-encapsulated fentanyl (50%) in 10 healthy volunteers. They found the maximum concentration of the inhaled fentanyl (1.15 ng/mL) to be significantly less than the IV dose (4.67 ng/mL; $P < 0.05$) and the time to maximal concentration to be prolonged (22.7 minutes for the aerosol vs 3.6 minutes for IV). The delayed pharmacokinetics of this formulation makes it unsuitable for the treatment of acute pain.

**Nebulized Morphine Pharmacokinetics**

Morphine as the prototypical opioid, has also been evaluated for the treatment of acute pain in nebulized form. Two studies have investigated the bioavailability of nebulized morphine in humans. Chrubasik et al\textsuperscript{25} reported the bioavailability of nebulized morphine given to 7 patients undergoing abdominal surgery. All patients were given 1 dose of 10 mg of nebulized morphine, and the bioavailability was compared with an equivalent dose of intramuscular morphine. The bioavailability of nebulized morphine was 16.6%, with a range of 8.9% to 34.6%. A similar study\textsuperscript{25} in 11 healthy volunteers compared 50 mg of nebulized morphine with 5 mg of IV and 10 mg of morphine oral elixir. Bioavailability was determined to be 24% ± 13% for nebulized morphine. Oddly, the researchers report a time to maximum serum concentration of 10 minutes with a SD of zero. This seems unlikely with 10 volunteers (1 dropout), considering the inherent biological variation involved. These data suggest that nebulized morphine has a much poorer bioavailability than nebulized fentanyl and probably reflects the greater lipid solubility of fentanyl as compared with morphine. Nebulized morphine continues to be utilized for the treatment of terminal dyspnea where a local opioid effect is likely more important than systemic absorption.\textsuperscript{28,29}

Table 1\textsuperscript{8,23,24,25,26} lists several key elements that can affect the absorption and pharmacokinetic parameters of nebulized fentanyl and morphine. Using an efficient aerosolizing device to deliver nebulized fentanyl is essential in ensuring a reliable and immediate availability of aerosolized fentanyl.
Table 1. Pharmacokinetic Parameters Associated With Nebulized Fentanyl and Morphine.

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Drug</th>
<th>Number of Participants</th>
<th>Aerosolized Device Used</th>
<th>Fentanyl or Morphine Dose(s) (µg)</th>
<th>Analytical Method</th>
<th>Reported Bioavailability</th>
<th>Maximum Fentanyl or Morphine Plasma Concentration (Mean ± SD)</th>
<th>Range of Time to Maximum Concentration (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MacLeod et al (2012)</td>
<td>Fentanyl</td>
<td>50</td>
<td>Staccato hand-held, single-dose oral inhaler (Alexza Pharmaceuticals, Palo Alto, CA)</td>
<td>25-300</td>
<td>Liquid chromatography and mass spectrometry</td>
<td>96.8%</td>
<td>25 = 4.7 ± 2.3 ng/mL, 50 = 5.7 ± 3.2 ng/mL, 100 = 5.5 ± 1.3 ng/mL, 150 = 6.0 ± 2.8 ng/mL, 300 = 8.2 ± 2.1 ng/mL</td>
<td>6-30 s (90% CI)</td>
</tr>
<tr>
<td>Mather et al (1998)</td>
<td>Fentanyl</td>
<td>10</td>
<td>SmartMist breath-actuated microprocessor-controlled oral inhaler (Aradigm Corp, Haywood, CA)</td>
<td>100-300</td>
<td>Gas chromatography and mass spectrometry</td>
<td>100%</td>
<td>100 = 2.8 ± 1.5 ng/mL, 200 = 5.7 ± 4.0 ng/mL, 300 = 7.2 ± 1.7 ng/mL</td>
<td>4-9 minutes (95% CI)</td>
</tr>
<tr>
<td>Worsley et al (1990)</td>
<td>Fentanyl</td>
<td>30</td>
<td>Acom II nebulizer at a flow rate of 8-10 L/min. Particle sizes of 2 µm or less (Becton-Dickinson Co, Franklin Lakes, NJ)</td>
<td>100 or 300</td>
<td>Radioimmunoassay</td>
<td>Not reported</td>
<td>300 = 0.4 ng/mL (SD not reported)</td>
<td>2 minutes (CI not reported)</td>
</tr>
<tr>
<td>Chrubasik et al (1988)</td>
<td>Morphine</td>
<td>7</td>
<td>Standard nebulizer particle sizes of 5 µm; oxygen flow of 5 L/min</td>
<td>10 mg</td>
<td>Radioimmunoassay</td>
<td>17% ± 13%</td>
<td>11.8 ± 42 ng/mL</td>
<td>45.5 ± 17.4 minutes</td>
</tr>
<tr>
<td>Masood and Thomas (1996)</td>
<td>Morphine</td>
<td>10</td>
<td>System 22 nebulizer driven by 6 L/min of oxygen flow</td>
<td>50 mg</td>
<td>High-performance liquid chromatography</td>
<td>24% ± 13%</td>
<td>23 ± 8 ng/mL</td>
<td>10 ± 0 minutes</td>
</tr>
</tbody>
</table>
Not all fentanyl formulations and aerosolized devices will result in rapid onset and complete bioavailability. Loss of drug through drug adherence to the inhaler device, on tubing, or tube spacers; aerosol deposition in the throat and trachea; or simply being swallowed can all result in loss of drug bioavailability. Improper use of inhalers can also result in ineffective therapy.

Efficacy of Nebulized Fentanyl in Acute Pain

The efficacy of nebulized fentanyl in postoperative analgesia was first investigated in anesthesiology as early as 1989. Worsley et al. performed a single-blinded, randomized, placebo-controlled study that evaluated the analgesic effects of nebulized fentanyl in 30 patients in a postoperative setting. The patients were given either 100 or 300 µg of nebulized fentanyl or normal saline as a control. After administration of the fentanyl, time to alternative analgesia was recorded for both fentanyl treatment groups and placebo. In addition, a linear visual analogue scale (VAS) was used to assess pain levels. Percentage reduction in pain scores were significantly different for fentanyl 300 and 100 µg versus placebo (73% vs 35%, P < 0.05). Time to alternative analgesia was also different (305 and 177 minutes vs 26 minutes, P < 0.05). Analgesia was significant from nebulized fentanyl despite low serum levels. No adverse effects were reported. A later double-blind, randomized study by Higgins analyzed 30 patients given 3 different doses of fentanyl base (190, 480, and 960 µg) in postoperative recovery. A placebo control was not used in the study. Efficacy of treatment was determined by a linear VAS, time to additional analgesia, and respiratory depression. Combined analysis of pain relief, time to further analgesia, and effect on respiratory frequency showed no difference between the 2 lower doses (190 and 480 µg) but a significantly more effective response from the 960-µg dose compared with the lower doses (P < 0.01). However, this was not reflected in the mean visual analogue scores, which were 6.5, 7.0, and 7.0 for the respective doses (190, 480, and 960 µg).

Controlled Clinical Trials

Miner et al. evaluated 41 patients (aged 6 months to 17 years) presenting to the emergency room with acute pain, using a convenience sampling technique. Among them, 14 patients were assigned to IV fentanyl (1.5 µg/kg) and 27 to nebulized fentanyl (3.0 µg/kg). Pain levels were measured at 0, 10, 20, and 30 minutes after the initial dose. Patients presented with acute pain from cellulitis (n = 3), abdominal pain (n = 4), burn (n = 5), laceration (n = 1), and extremity fracture/contusion (n = 28). Four patients in the IV fentanyl group were switched to the nebulized fentanyl group after the parents requested that their children receive nebulized fentanyl treatment. Of 10 patients who received IV treatment, 5 (50%) patients and 23 out of 31 (74%) who received nebulized fentanyl treatment were described as having pain adequately treated by their physician. Five patients were withdrawn from the study because of inadequate initial pain control: 4 from the nebulized group and 1 from the IV treatment group. Patients withdrawn from the nebulized groups were all younger than 3 years of age. The authors noted that these younger children were unable to get a proper seal with their mouth around the breath-actuated nebulizer system and were consequently unable to receive any medication. There were no adverse events reported for this study (see Table 2).

Singh et al. conducted a prospective, double-blind, controlled, randomized clinical trial that focused on the treatment of pain with nebulized fentanyl in adult patients undergoing lower-abdominal surgery. A total of 90 individuals were enrolled in this study and randomized into 3 separate groups: IV fentanyl 2 µg/kg, nebulized fentanyl 3 µg/kg, and nebulized fentanyl 4 µg/kg. The VAS pain score was utilized and assessed at baseline, 5, 10, 15, 30, 45, 60, 90, and 120 minutes. Any patients not relieved from pain after 15 minutes of treatment with any group were given 15 mg/kg IV acetaminophen and excluded from the study. Overall, both doses of nebulized fentanyl were significantly more effective (P < 0.005) based on mean VAS changes from 5 minutes until 15 minutes in comparison with baseline. It is noteworthy that the duration of pain relief was prolonged in the nebulization groups compared with the IV group (90 vs 30 minutes, respectively), and the onset of analgesia was delayed in the nebulized fentanyl group compared with the IV group (10 vs 5 minutes). There were no reports of clinically significant hemodynamic instability or respiratory depression. To assess adverse effects, a Ramsay sedation scoring system was utilized during the study. Sedation scores were significantly higher in the IV fentanyl group versus the nebulized fentanyl group at 5, 10, and 15 minutes (P < 0.001). No differences were found in postoperative nausea and vomiting, pruritus, hypoxia, urinary retention, or bradycardia between the 3 groups.

Farahmand et al. conducted a double-blind, randomized clinical trial evaluating the pain relief of 90 patients (age = 15-50 years) with limb pain. Patients were randomized to either nebulized fentanyl or IV morphine within the emergency department. A total of 47 patients received treatment with 4 µg/kg nebulized fentanyl, whereas 43 patients received treatment with 0.1 mg/kg IV morphine. A Numerical Rating Scale (NRS) was used to assess pain at baseline and at 10, 15, 30, 45, and 60 minutes after medication administration. A rescue dose of 1 mg of morphine was given to patients in either group if the NRS score remained at 5 or more for at least 15 minutes. This rescue dose was given in 5-minute intervals until the NRS score dropped to
<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Number of Participants</th>
<th>Study Design</th>
<th>Participants (study details)</th>
<th>Drugs and Doses Used</th>
<th>Outcomes</th>
<th>Adverse Events</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bartfield et al (2003)</td>
<td>50</td>
<td>Double-blind, randomized, double-placebo controlled</td>
<td>Adults (18 years of age or older), nonspecific abdominal pain</td>
<td>Nebulized fentanyl 1.5 µg/kg, IV fentanyl 1.5 µg/kg</td>
<td>Statistically significant decrease in pain at 15 minutes for NF over IVM (P &lt; 0.05) but not at 30 minutes using a VAS. No difference in need for rescue analgesia between the groups.</td>
<td>No major adverse events</td>
<td>Protocol violations; 3 patients waited 20-25 minutes between 2 of their pain scales; 1 patient received a wrong dose (1 µg/kg) of fentanyl, 1 patient reported no pain at baseline, and 1 patient was younger than 18 years</td>
</tr>
<tr>
<td>Miner et al (2007)</td>
<td>41</td>
<td>Randomized, prospective, controlled, unblinded</td>
<td>Children (aged 6 months to 17 years), acute pain from extremity fracture (n = 28), burns (n = 5), abdominal pain (n = 4), cellulitis (n = 3), and laceration (n = 1)</td>
<td>Nebulized fentanyl 3.0 µg/kg, IV fentanyl 1.5 µg/kg</td>
<td>There was no difference in pain relief between the 2 treatments as perceived by the treating physicians (P = 0.42) or by the patients (P = 0.28) using a VAS and CHEOPS pain scale</td>
<td>No major adverse events</td>
<td>Questionable randomization; patients switched groups after initially being randomized. Nine patients withdrew from study. 4 of these patients were &lt;3 years old and could not trigger the breath-actuated nebulizer</td>
</tr>
<tr>
<td>Furyk et al (2009)</td>
<td>77</td>
<td>Randomized, prospective, controlled, unblinded</td>
<td>Children (aged 4-13 years old), clinically suspected, limb pain</td>
<td>Nebulized fentanyl 4 µg/kg, IV morphine 0.1 mg/kg</td>
<td>Decrease in pain levels were statistically significant for both NF and IVM (P &lt; 0.0001) at 15 and 30 minutes, using a WBFPS</td>
<td>Abdominal pain, nausea, rash reported in 1 patient in the IVM group</td>
<td>Treating physicians judged the response of the treatment; 5 patients were withdrawn from the study; 1 patient was withdrawn because of inadequate analgesia; I was excluded when age found to be too low</td>
</tr>
<tr>
<td>Singh et al (2013)</td>
<td>90</td>
<td>Prospective, randomized, double-blind</td>
<td>Adults (aged 20-40 years), lower-abdominal surgery</td>
<td>Nebulized fentanyl 3 µg/kg, IV morphine 2 µg/kg</td>
<td>Statistically significant average VAS change began at 5 minutes and continued until 15 minutes as compared with baseline (P &lt; 0.005)</td>
<td>No major adverse events in any group; no statistical significance in control or experimental groups</td>
<td>Total concentration not measured; total nebulized fentanyl consumption in 24 hours not recorded. Patients consisted of those with lower-abdominal pain, so the results of this study cannot be applied to certain other types of patients. Study consisted of a small sample size</td>
</tr>
<tr>
<td>Farahmand et al (2014)</td>
<td>90</td>
<td>Randomized, double-blind</td>
<td>Adults (age 15-50 years); acute pain, limb trauma divided into 3 categories; wound and soft tissue, fractures, sprains, and strains</td>
<td>Nebulized fentanyl 4 µg/kg, IV morphine 0.1 mg/kg</td>
<td>Pain scores were similar between NF and IVM at 5, 10, and 15 minutes; NF significantly better at 30 minutes (P &lt; 0.05), 45 and 60 minutes (P &lt; 0.0001) using a NRS</td>
<td>No major adverse events for the fentanyl group, IV morphine group: 4 patients presented with nausea, vertigo, and slight decrease in consciousness</td>
<td>Patients only observed for up to 1 hour postadministration. NF statistically better than IVM at 30, 45, and 60 minutes but not likely clinically significant</td>
</tr>
<tr>
<td>Abd El-Hamid et al (2015)</td>
<td>87</td>
<td>Randomized, prospective, comparative</td>
<td>Adults (age 15-56 years old), postoperative reconstruction surgery pain</td>
<td>Nebulized fentanyl 4 µg/kg, IV fentanyl 2 µg/kg</td>
<td>Onset of analgesia more rapid with IVF and longer with NF (P &lt; 0.05) using a VAS</td>
<td>Significantly greater incidence of bradycardia occurred in the IVF group (n = 4) than in the NF group (n = 0; P &lt; 0.05)</td>
<td>Both groups (IVF and NF) experienced nausea, vomiting, and pruritus, although it was less frequent in the NF group</td>
</tr>
<tr>
<td>Deaton et al (2015)</td>
<td>40</td>
<td>Randomized, double-blind, double-placebo-controlled</td>
<td>Adults (aged 18-65 years old), acute abdominal pain</td>
<td>Nebulized fentanyl 2 µg/kg, IV morphine 0.1 mg/kg</td>
<td>Statistical significance for patient, physician satisfaction, and need for rescue medication in NF over IVM</td>
<td>No adverse events observed in NF or IVM patient groups</td>
<td>Eight patients removed from final data: 6 patients removed because of discrepancies found on consent form; 2 patients not included in analysis because they received incorrect doses of medication. Study length was inadequate; because of peak effect time of medications, bias toward fentanyl may have resulted. Differences in smell between NF and IVM could have affected blinding</td>
</tr>
</tbody>
</table>

Abbreviations: CHEOPS, Children’s Hospital of Eastern Ontario Pain Scale; IV, intravenous; IVM, IV morphine; NF, nebulized fentanyl; NRS, Numerical Rating Scale; VAS, Visual Analog Scale; WBFPS, Wong and Baker Faces Pain Scale.
lower than 5. The study reports that 4 patients in the nebulized group and 3 patients in the IV morphine group received a rescue dose. Both IV morphine and nebulized fentanyl produced quality pain management in severe limb pain, which they quantify as NRS <5, for the first 60 minutes, with a quantified reduction in NRS >3 after 5 minutes. However, there was no statistical difference between therapies until 15 minutes postadministration \( (P = 0.011) \). This statistical difference continued until the last monitored time of 60 minutes \( (P = 0.0001) \). No adverse effects were reported for the patients receiving nebulized fentanyl; however, 4 patients in the IV morphine group experienced nausea, vertigo, and a decrease in consciousness \( (P = 0.048) \). Patient satisfaction with analgesia was assessed using a 6-item Likert rating scale; satisfaction was not significantly different between the groups \( (P = 0.67) \).

Bartfield et al\(^{17}\) compared the efficacy of nebulized fentanyl with IV fentanyl in patients presenting to the emergency department with nonspecific abdominal pain. The study consisted of 50 randomized individuals, 24 receiving IV treatment \( (1.5 \, \mu g/kg) \) and 26 receiving nebulized treatment \( (1.5 \, \mu g/kg) \) in a double-placebo control design. Each patient’s pain score was measured, using a VAS, at baseline and reassessed at 15 and 30 minutes after administration of the medication. No statistical difference was found in pain scores at 30 minutes after treatment \( (P = 0.24) \); however, IV fentanyl pain scores were significantly less after 15 minutes of treatment \( (P = 0.005) \). In all, 50% of patients required rescue medication in the IV treatment group and 69% in the nebulized treatment group \( (P = 0.25) \). No serious adverse effects were observed.

Furyk et al\(^{18}\) studied the efficacy of nebulized fentanyl \( (4 \, \mu g/kg) \) in comparison to IV morphine \( 0.1 \, mg/kg \) in a randomized controlled trial of 73 children 4 to 13 years old. Patients were randomized if presenting to the emergency department with suspected limb fractures \( (79\% \, \text{radius/ulna}, 10\% \, \text{humerus}, 5.5\% \, \text{tibia/fibula}, \text{and} 5.5\% \, \text{other}) \). Pain was assessed at 0, 15, and 30 minutes using the Wong and Baker Faces Pain Scale. No statistical difference in pain scores were observed between IV morphine and nebulized fentanyl treatment groups at 15 or 30 minutes \( (P \approx 0.34 \text{ and } 0.081, \text{respectively}) \). Although not statistically significant, the nebulized fentanyl pain scores trended down over time suggesting perhaps a slightly more prolonged analgesia effect versus IV morphine. This study claims that noninferiority of nebulized fentanyl compared with IV morphine was met in relation to the CONSORT definition. No adverse effects were observed in the fentanyl group, but 3 patients in the morphine group did report adverse effects consisting of abdominal pain and nausea, and 1 patient had a rash. One patient was withdrawn from the nebulized group because of inadequate analgesia treatment as determined by the overseeing physician. This patient’s information was included assuming no change in pain score, and it had no statistical effect on end results.

Abd El-Hamid et al\(^{16}\) compared nebulized fentanyl \( (4 \, \mu g/kg) \) and IV fentanyl \( (2 \, \mu g/kg) \) for postoperative analgesia in a prospective, randomized, double-blind, comparative study. A total of 87 adult patients \( (18-56 \, \text{years}) \) underwent unilateral arthroscopic anterior cruciate ligament reconstruction surgery and were assessed using a VAS for their pain. Onset and duration of analgesia, duration of surgery, number of patients not relieved of pain at 15 minutes after analgesia administration, level of sedation (Ramsay Sedation score), and adverse effects were all recorded as parameters. Nebulized fentanyl demonstrated a delay in onset of analgesia \( (P = 0.023) \) but produced a longer duration of action in comparison to the IV fentanyl group \( (P = 0.014) \). Although these values were statistically significant, they do not appear to be clinically significant. The values depicted within the table provided showed an onset of analgesia within \( 4.55 \pm 1.18 \) minutes for the IV group and \( 5.13 \pm 1.16 \) minutes for the nebulized group. The duration of analgesia scores were presented as \( 74.7 \pm 9.81 \) minutes and \( 80.5 \pm 11.52 \) minutes, respectively. Patients requiring rescue medications at 15 minutes were similar between the 2 groups \( (\text{NF} = 23.8\% \, \text{vs IVF} = 24.4\%) \). A statistically significant increase in bradycardia was seen in the IV group compared with the nebulized group. The IVF patients experienced maximum sedation at 5 minutes, with the NF patients having a more gradual rise in sedation over time but with Ramsey sedation scores less than those of the IVF group. Other adverse effects that were recorded included the following: respiratory depression (observed in the IV group only), postoperative nausea and vomiting, and pruritus (in both groups).

### Discussion

Acute pain in patients presenting to the emergency room is a common occurrence. Timely and accurate assessment of the etiology of the pain is an essential first step.\(^ {32}\) Guidelines and consensus statements for the treatment of acute pain in the emergency room setting almost universally include an opioid analgesic.\(^ {33,34}\) IV morphine, or other similar opioid, would be considered the gold standard comparison against which new approaches should be compared. The available clinical trial data\(^ {4,15,16,18,30,31}\) suggest that nebulized fentanyl is at least equally effective as IV opioids for acute pain in the emergency room setting. However, these controlled trials have been of short duration with standardized preparation, administration, and monitoring of nebulized fentanyl. A number of questions still remain regarding widespread clinical use of nebulized fentanyl for acute pain management.

Inhalation of fentanyl is a noninvasive method of administering a potent opioid analgesic. This route has been demonstrated to result in rapid absorption and resultant pain relief. However, there are situations where inhalation of a
drug would not likely be the preferred route of administration. Patients with head and neck surgery, orofacial trauma, and uncooperative or agitated patients would not be good candidates for nebulized fentanyl. In addition, children younger than 3 years clearly can have difficulty with a breath-actuated nebulizer and are probably not good candidates for nebulized fentanyl.

The ability of a drug to reach the distal airways is dependent on several key physiological and anatomical factors such as the ability to generate adequate inspiratory effort, the patency of the airways, a sealed thoracic wall, and sufficient respiratory drive. There are also a number of disease processes, drugs, and environmental factors that could affect the disposition of nebulized drug to these distal sites. The effect of chronic smoking on the rate and extent of fentanyl absorption has not been studied. Restrictive, obstructive, or inflammatory lung disease; degree of mucous plugging; and bronchoconstrictive pharmacotherapy may also affect the efficacy of fentanyl delivered by inhalation.

None of these factors has been studied with this route of fentanyl administration and remain potential limitations.

Aerosol drug delivery, although seemingly simple in concept, is actually a complex phenomenon. There are several critical factors that can affect the consistent delivery of drug to the terminal airways. Particle size can determine how a drug deposits into different parts of the lung. Optimum particle size is generally recognized as being between 1 and 4 µm. Particles less than 1 µm in size are generally exhaled without being deposited in the lung. Particles greater than 5 µm in size are often deposited in the delivery device, swallowed, or deposited in the upper airway, possibly decreasing the rate and extent of absorption. Second, there are 4 major types of nebulizer systems available: ultrasonic, jet, vibrating mesh-aperture plate, and breath-enhanced jet nebulizers. Although it is not clear which type of nebulizer might be optimum for fentanyl administration, variation in the types of nebulizers, within the same brand and across different brands, complicates this issue significantly. Finally, drug preparation is central to effective aerosol delivery. Nebulized medications should be sterile, isotonic, pH balanced, and pyrogen free. Ideally, it should be preservative free and not have an unpleasant taste or odor, which could decrease patient acceptance. At present, nebulized fentanyl is not available commercially and is usually prepared using the IV preparation and given by nebulization. All the factors previously mentioned could potentially result in inconsistent efficacy of nebulized fentanyl for the treatment of acute pain.

Very few adverse effects were reported in these clinical trials. The short duration of these studies may account for the lack of observable adverse effects from nebulized fentanyl, but adverse effects of opioid analgesics are predictable and common. Respiratory depression, constipation, euphoria, dysphoria, sedation, bradycardia, convulsions, nausea, vomiting, pruritus, and miosis are all extensions of opioid pharmacology. Fentanyl has been shown to have significantly less histamine release, and resultant hemodynamic instability, than morphine, hydromorphone, or meperidine. However, the full range and magnitude of potential adverse effects from nebulized fentanyl are not known at this time. The abuse potential of nebulized fentanyl would be another factor to be considered. The rapid onset and high bioavailability of a nebulized fentanyl product would likely make it a potential source of diversion. Opioid abuse continues to be a major public health issue in the United States, and addiction-related illness has required increasing amounts of health care resources for treatment and prevention.

Additional applications for nebulized fentanyl include its potential use in breakthrough pain and dyspnea. Although inhaled morphine and furosemide have been widely used for refractory dyspnea, nebulized fentanyl has shown efficacy in one controlled trial and a case report. More evidence will be necessary before it could be recommended for terminal dyspnea. Another potential application of nebulized fentanyl is in the management of breakthrough pain. Because of the wide variety of rapid-onset dosage forms available for fentanyl (transmucosal, sublingual spray, sublingual tablet, and intranasal), it is widely utilized for breakthrough pain.

Nebulization offers another route of fentanyl administration that provides a quick onset of action and is noninvasive. The noninvasive aspect of this analgesic administration could be highly useful in the pediatric population presenting with acute or chronic pain. This would allow analgesic coverage while avoiding additional pain, discomfort, and stress associated with IV analgesic administration.

A potential application of nebulized fentanyl could also be in patients with terminal cancer and patients in hospice care. Both situations require long-term pain control in settings that may not require constant IV access. Pain control through nebulized fentanyl might be particularly helpful in breakthrough pain because of the rapid onset of analgesia through this noninvasive route of administration. Additional clinical trials and experience will be necessary before this can be routinely adopted. The use of this route within the inpatient setting could benefit patients by decreasing the discomfort associated with parenteral analgesia and decrease the incidence of extravasation associated with IV drug administration. Nebulized fentanyl could potentially be easier to administer for hospital staff in comparison with IV administration. However, IV access in the inpatient setting is often necessary in medically unstable patients, where emergency administration of life-saving drugs may require immediate vascular access.

**Conclusion**

Nebulized fentanyl appears to be as efficacious as IV opioids for the treatment of acute pain, with few adverse effects,
although the total number of participants in all trials is small (n = 583). It is not currently available as a commercial product and must be extemporaneously prepared. Therapeutic efficacy with nebulized fentanyl requires a consistently prepared product and nebulization device that will reliably deliver the drug to the patient’s distal airways. A nebulized fentanyl product would also have abuse potential.

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