Nebulized versus intravenous fentanyl for postoperative analgesia after unilateral arthroscopic anterior cruciate ligament reconstruction surgery: a prospective, randomized, comparative trial
Ahmed M. Abd El-Hamid, Mohamed A.I. Elrabeie, Ehab E. Afifi

Department of Anesthesia and ICU, Faculty of Medicine, Benha University, Benha, Egypt

Correspondence to Ahmed M. Abd El-Hamid, MD, 20 Ezz Eldin Omar Street, Elharam, Giza, 12111, Egypt
Tel: +20 100 520 4130; fax: 0233862999; e-mail: bashaahmad@yahoo.com

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Introduction
Fentanyl is a potent, synthetic opioid analgesic with a rapid onset and short duration of action. It is a strong agonist at the μ-opioid receptors. Fentanyl is the most frequently used opioid in clinical anesthesia today. It was first synthesized in 1960. It is structurally related to the phenylpiperidines and has a clinical potency rate that is 50–100 times greater than that of morphine [1].

Intravenous route for fentanyl administration has been the gold standard for anesthesia and analgesia. However, it is often associated with several side effects [2]. Alternative routes of administration are now available; one of them could be inhalational drug delivery. Fentanyl being highly lipophilic is suitable for use through this route, and inhalational administration could be a new promising noninvasive method for fentanyl administration [3]. This study aimed to compare the effect of nebulized fentanyl with intravenous fentanyl for postoperative analgesia after unilateral arthroscopic anterior cruciate ligament reconstruction surgery.

Patients and methods
A total of 87 patients scheduled for unilateral arthroscopic anterior cruciate ligament reconstruction surgery under regional anesthesia were enrolled in the study and were randomly allocated into two groups. Group IV included 42 patients who received 2 μg/kg of fentanyl intravenously, and Group N included 45 patients who received 4 μg/kg of fentanyl nebulization using a standard ventimask. Both groups received the analgesic drug through either intravenously or nebulization route whenever the patient reported pain for the first time in the postanesthesia care unit that was of a score greater than 4 on the visual analog scale. Observations were made for the onset and duration of analgesia, number of patients who were not relieved of pain even 15 min after analgesia administration, level of sedation using the Ramsay sedation scale, and side effects.

Results
Both groups were similar in terms of demographic characteristics and duration of surgery. The onset of analgesia was significantly delayed in group N in comparison with group IV, whereas the duration of analgesia was significantly longer in group N in comparison with group IV. In group IV, the Ramsay sedation score was the maximum at 5 min. In group N, there was a slow rise in the sedation score, but it was always less than that in group IV. Side effects in group N were less compared with group IV, and the number of patients who developed bradycardia was significantly higher in group IV.

Conclusion
This study showed that nebulization with fentanyl is a good alternative to intravenous fentanyl for adequate postoperative pain relief with fewer side effects.

Keywords:
intravenous fentanyl, nebulized fentanyl, postoperative analgesia
Patients with morbid obesity (BMI >30), respiratory diseases, hepatic and/or renal diseases, coagulation disorders, pregnant or breast feeding women, uncooperative patients, patients with hypersensitivity to opioids, patients taking other narcotic pain medicines (e.g. morphine, codeine) on a regular schedule or those taking drugs that may interfere with the action of fentanyl (e.g. sibutramine, sodium oxybate, or monoamine oxidase inhibitor) were excluded from the study.

These patients were randomly allocated using the sealed envelope method into two groups.

Group IV included 42 patients who received 2 μg/kg of fentanyl diluted in 10 ml of normal saline 0.9% intravenously along with 5 ml of normal saline 0.9% nebulized using a standard ventimask at a constant flow rate of oxygen at 8–10 l/min for 10 min.

Group N included 45 patients who received 10 ml of normal saline 0.9% intravenously along with 4 μg/kg of fentanyl in 5 ml of normal saline 0.9% nebulized using a standard ventimask at a constant flow rate of oxygen at 8–10 l/min for 10 min.

Both groups received spinal anesthesia with 12.5 mg bupivacaine through a 25 G spinal needle. The block level was between T8 and T10.

Both groups received the analgesic drug through either intravenous or nebulization routes whenever the patient reported pain for the first time in the postanesthesia care unit that was of a score greater than 4 on the visual analog scale (VAS).

The following parameters were recorded:

1. Duration of analgesia (primary outcome): The time from the completion of analgesia until the patient’s second request of analgesia.
2. Onset of analgesia: the time from the completion of analgesia (intravenous or nebulization) until VAS became equal or less than 2.
3. Duration of surgery: The time from skin incision until removal of surgical drapes.
4. Number of patients who were not relieved of pain even after 15 min of analgesia administration (VAS>4). These patients received diclofenac sodium 75 mg intramuscularly.
5. Level of sedation using the Ramsay sedation scale (Table 1) was recorded initially every 5 min up to 30 min, and then at intervals of 15 min up to 2 h.
6. Side effects:
   a. Nausea and vomiting.
   b. Bradycardia (heart rate < 60/min).
   c. Respiratory depression (respiratory rate < 8 min).
   d. Hypotension (mean arterial pressure <50).
   e. Pruritus.
   f. Bronchospasm.

### Statistical analysis

Data were managed using SPSS (IBM, New York, USA), version 16. Quantitative data were presented as mean and SD and were analyzed using the Student t-test. Qualitative data were presented as number of patients and percentages and were analyzed using the \( \chi^2 \) and Z-tests. Ramsay sedation scores were presented as median and interquartile range and were analyzed using the Mann–Whitney \( U \)-test. A \( P \)-value less than 0.05 was considered to be statistically significant, whereas a \( P \)-value less than 0.01 was considered to be statistically highly significant. Sample size was estimated according to a pilot study for the first 10 patients in each group by assuming \( \alpha \) error = 0.05 (two tailed) and a power of 80% to detect an assumed clinically significant difference (effect size \( d = 0.664 \)) between the paired measurements of the duration of analgesia between the two groups (primary outcome). The \( t \)-test for matched pairs was used to estimate the sample size. Thirty-seven patients were estimated in each group.

### Results

Both groups were similar in terms of demographic characteristics, duration of surgery, and the number of patients who required analgesia. The onset of analgesia was significantly delayed in group N in comparison with group IV, whereas the duration of analgesia was significantly longer in group N in comparison with group IV (Table 2).

In group IV, the Ramsay sedation score was the maximum at 5 min. In group N, there was a slow rise in the sedation score, but it was always less than that in group IV (Fig. 1).

Side effects in group N were less compared with group IV, and the number of patients who developed bradycardia were significantly higher in group IV (Table 3).
Th e present study compared the eff ect of fentanyl 2 μg/kg through intravenous route with the eff ect of fentanyl 4 μg/kg by nebulization on the basis of a study conducted by Singh et al. [2], which showed that 4 μg/kg nebulized fentanyl produces pain relief comparable to 2 μg/kg intravenous fentanyl. Th e onset of analgesia in the present study showed a signifi cant delay in group N in comparison with group IV, whereas the duration of analgesia was signifi cantly longer in group N in comparison with group IV. Although these diff erences have no clinical value, nebulization with fentanyl had fewer side eff ects. Th is was in accordance with the fi ndings of Singh et al. [2] and Bartfi eld et al. [5]. Th is was also supported by Kissin [6], who found that maximum serum concentration of fentanyl is reached rapidly after intravenous administration compared with intranasal administration. Th e previous fi nding also explains the diff erence in sedation score between the intravenous group and the nebulization group in our study. Side eff ects were less in group N. Th is was in accordance with Worsley et al. [3] and Higgins et al. [7]. In a study conducted by MacLeod et al. [8], they demonstrated that the pharmacokinetic profi le of single doses of inhaled fentanyl is comparable to that of intravenous administration.

Farahmand et al. [9] compared the eff ectiveness of nebulized fentanyl with intravenous morphine in the management of acute limb pain and suggested that nebulized fentanyl is a rapid, safe, and eff ective method for temporary control of acute limb pain in emergency department patients. Furyk et al. [10] also compared the effi  cacy of nebulized fentanyl with intravenous morphine in pediatric patients presenting to the emergency department with clinically suspected limb fractures and found that nebulized fentanyl at a dose of 4 μg/kg provided a clinically signifi cant improvement in pain scores, comparable to that of intravenous morphine. Several studies [2,5,11] have documented the eff ectiveness of nebulized fentanyl compared with intravenous fentanyl.

**Conclusion**

Nebulization with fentanyl is a good alternative to intravenous fentanyl for adequate postoperative pain relief with fewer side eff ects.

**Acknowledgements**

**Conflicts of interest**

None declared.

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**Table 2** Demographic characteristics, duration of surgery, and onset and duration of analgesia

<table>
<thead>
<tr>
<th>Title</th>
<th>Group IV</th>
<th>Group N</th>
<th>Test</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>39.5 ± 9.8</td>
<td>40.35 ± 11.5</td>
<td>t = 0.35</td>
<td>0.72</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>80.4 ± 6.34</td>
<td>83.1 ± 7.71</td>
<td>t = 1.7</td>
<td>0.08</td>
</tr>
<tr>
<td>Sex (male : female)</td>
<td>32 : 10</td>
<td>33 : 12</td>
<td>χ² = 0.09</td>
<td>0.75</td>
</tr>
<tr>
<td>ASA (I : II)</td>
<td>29 : 13</td>
<td>30 : 15</td>
<td>χ² = 0.05</td>
<td>0.8</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>112.4 ± 9.45</td>
<td>116.1 ± 8.81</td>
<td>t = 1.9</td>
<td>0.062</td>
</tr>
<tr>
<td>Onset of analgesia (min)</td>
<td>4.55 ± 1.18</td>
<td>5.13 ± 1.16</td>
<td>t = 2.3</td>
<td>0.023*</td>
</tr>
<tr>
<td>Duration of analgesia (min)</td>
<td>74.7 ± 9.81</td>
<td>80.5 ± 11.52</td>
<td>t = 2.5</td>
<td>0.014*</td>
</tr>
<tr>
<td>Patients who required analgesia [n (%)]</td>
<td>10 (23.8)</td>
<td>11 (24.4)</td>
<td>Z = 0.07</td>
<td>0.94</td>
</tr>
</tbody>
</table>

Data are presented as mean and SD, except for sex and ASA, which are presented as numbers; ASA, American society of anesthesiologists; IV, intravenous; N, nebulization; *Statistically signifi cant difference.

**Table 3** Comparison between groups as regards side eff ects

<table>
<thead>
<tr>
<th>Title</th>
<th>Group IV</th>
<th>Group N</th>
<th>Z value</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PONV</td>
<td>4 (9.5)</td>
<td>1 (2.2)</td>
<td>1.46</td>
<td>0.14</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>4 (9.5)</td>
<td>0</td>
<td>2.11</td>
<td>0.03*</td>
</tr>
<tr>
<td>Respiratory depression</td>
<td>1 (2.3)</td>
<td>0</td>
<td>1.04</td>
<td>0.29</td>
</tr>
<tr>
<td>Hypotension</td>
<td>0</td>
<td>0</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Pruritus</td>
<td>4 (9.5)</td>
<td>2 (4.4)</td>
<td>0.93</td>
<td>0.35</td>
</tr>
<tr>
<td>Bronchospasm</td>
<td>0</td>
<td>0</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Data are presented as n [%]; IV, intravenous; N, nebulization; PONV, postoperative nausea and vomiting; *Statistically signifi cant difference.

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**Discussion**

Th e present study compared the eff ect of fentanyl 2 μg/kg through intravenous route with the eff ect of fentanyl 4 μg/kg by nebulization on the basis of a study conducted by Singh et al. [2], which showed that 4 μg/kg nebulized fentanyl produces pain relief comparable to 2 μg/kg intravenous fentanyl.

Figure 1

Ramsay sedation scale. Data were represented as median and interquartile range. *Signifi cant; **Highly signifi cant.
References


