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Brief Report

A randomized controlled trial comparing the effect of intravenous, subcutaneous, and intranasal fentanyl for pain management in patients undergoing cesarean section

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Abstract

Background: The objective of this study was to evaluate and compare the effects of three methods of using intravenous (IV), subcutaneous and intranasal (IN) fentanyl for pain management following general anesthesia in patients undergoing cesarean section.

Materials and Methods: A prospective, randomized, single-blind clinical trial was done on 75 patients aged 20–40 years, American Society of Anesthesiology-1, who had a normal singleton pregnancy beyond 36 weeks of gestational age. Patients were randomized to receive 50 μg fentanyl intravenously (Group 1), subcutaneously (Group 2) or intranasally (Group 3) after closure of incision. The pain intensity, nausea, the systolic, and diastolic blood pressures were assessed.

Results: All groups were equivalent for baseline characteristics. The average pain visual analog scale (VAS) score was less in the second group who received fentanyl subcutaneously at the time of recovery admission (6.8 ± 1.5) ($P = 0.037$) and after 3 h (6.36 ± 1.5) ($P = 0.033$) postoperatively. The mean VAS score of nausea and the mean systolic and diastolic blood pressures were not significantly different between three groups throughout the study ($P > 0.05$).

Conclusion: subcutaneous fentanyl is an effective alternative to IV and IN route of administration for pain management.

Key Words: Fentanyl, intranasal, intravenous, subcutaneous, visual analog scale

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INTRODUCTION

Cesarean section is the most common main women surgery carried out worldwide.[1] The prevalence of cesarean section worldwide was 15% and in the developed world was 21.1%.[2] In the UK in 2008, cesarean rates of up to 31.9% have been reported and in the USA more than 1 million are believed to be performed annually.[3,4] In Iran, 35.0% of deliveries were by cesarean section.[5]

The optimum form of postoperative analgesia for cesarean section is not well known, but opioids continue to be the main pharmacological treatment

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for severe acute pain. Conventional routes of opioid administration consist of oral, intramuscular, and subcutaneous are helpful in controlling pain if the treatments are individualized and dosages are titrated to effect.[6] Nasal administration of opioids possibly is an option for intravenous (IV), transmucosal and subcutaneous analgesia administration in a number of patients and it is a subject on which attention is focused.[7,8] Different doses of fentanyl (75, 100, 150, or 200 μg) by both the intranasal (IN) and IV routes were compared for the management of acute pain in patients undergoing molar extractions. The onsets and durations of analgesia were not significantly different between single doses of IN and IV fentanyl (INF and IVF, respectively) in these adult patients.[9] Furthermore, in the postoperative period in patients undergoing surgery for abdominal, orthopedic, or thyroid surgery, INF was an effective alternative to IVF in postoperative patients.[10]

Fentanyl is a strong m-opioid receptor agonist with a relatively low molecular weight and (unlike morphine) lipophilic characteristics, which makes it appropriate for transmucosal administration e.[11] On the other hand, IN administration of fentanyl results in a time to onset of action comparable to IV administration and cause pain relief with lower maximum plasma concentrations comparable to IV administration and results in lower rates of adverse events such as nausea, vomiting, and respiratory depression.[12]

To our knowledge, no study compares the effect of three routes of fentanyl administration for pain management. The aim of this study was to evaluate the use of IV, subcutaneous and INF for pain control in patients undergoing cesarean section.

MATERIALS AND METHODS

This prospective, randomized, single-blind clinical trial was conducted in Shahid Beheshti Hospital in Isfahan, Iran. The study protocol was approved by the Anesthesiology Department and Ethic Committee of Isfahan Medical University and written informed consent was obtained from 75 healthy parturients with normal singleton pregnancy beyond 36 weeks of gestational age. Eligible subjects were American Society of Anesthesiology-1, 20–40 years of age, undergoing cesarean section following general anesthesia with no history of substance abuse, drug hypersensitivity, blocked or traumatized nose, psychiatric or neurologic impairment (to be unable to do pain scoring) and not refusing nasal administration of the drug. Patients were randomized with the use of randomization tables to three groups (25 patients in each group).

After enrollment, every patient was weighed on the same scale. In the operating room, routine monitors including noninvasive blood pressure, electrocardiogram, pulse oximeter, and capnogram were attached to the patients and vital signs were recorded. All patients in three groups received similar induction and maintenance of anesthesia. General anesthesia was induced with 5 mg/kg thiopental sodium given over 10–15 s, after preoxygenation for 5 min. An assistant applied cricoid pressure from the time of induction of anesthesia until the airway was secured. Laryngoscopy and tracheal intubation were performed 60 s after giving 1.5 mg/kg succinylcholine. Anesthesia was maintained with 50% nitrous oxide in oxygen and 1.2% isoflurane. Atracurium was used for muscle relaxation. $EtCO_2$ was maintained at 33–40 mmHg throughout surgery. After delivery of the baby, analgesia was provided by 0.1 mg/kg morphine, and 20 IU IV Syntocinon in 1 L Ringer's lactate was infused to initiate uterine contraction.

Toward the end of the surgery, after closure of cesarean incision, patients were randomly placed in one of these three treatment groups:

1. Group 1: Patients received 50 μg fentanyl intravenously
2. Group 2: Patients received 50 μg fentanyl (1 ml) subcutaneously on anterior abdominal wall
3. Group 3: Patients received 50 μg fentanyl (1 ml) intranasally. In this method, the patient should be reclining at 45° and the syringe should be held horizontal and the contents expelled as a mist into the nares in one rapid dose and not ask the patient to sniff. Dose of 1 ml should be divided between nares.

An anesthetist who administered fentanyl did not interfere in data collection.

After completion of surgery, the residual effects of neuromuscular blockade were reversed with 0.05 mg/kg neostigmine and 0.02 mg/kg atropine.

At the time of admission to the recovery room and then for every 30 min, until 4 h postoperatively, the pain intensity and nausea were assessed by visual analog scale (VAS), ranging from 0 (no pain) to 10 (worse pain). If analgesia was considered inadequate and VAS for pain was >4 the meperidine (1 mg/kg) were administered by an anesthesiologist. The systolic and diastolic blood pressures were measured and recorded before induction of anesthesia (baseline), before fentanyl administration and then at 5, 15, and 30 min later in the recovery room.

All data were collected and recorded by an anesthetist who was not aware of the method of intervention.

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Data were analyzed using the SPSS version 20 (SPSS Inc., Chicago, Illinois, USA). Assuming a 5% significance level ($\alpha = 0.05$) and power of 80% ($\beta = 0.20$) to detect 1.3 differences in VAS score between three groups, a sample size of 25 patients per group was required. Statistical analysis was performed by using analysis of variance test, Chi-square test and Kruskal–Wallis tests. A $P < 0.05$ was considered statistically significant.

RESULTS

A total of 75 patients were randomized during the study period. All of the patients completed the study and were evaluable. As shown in Table 1, the baseline characteristics of patients were equivalent. The average pain VAS score was less in the second group who received fentanyl subcutaneously at the time of recovery admission (6.8 ± 1.5) ($P = 0.037$) and after 3 h (6.36 ± 1.5) ($P = 0.033$) [Table 2]. The mean of VAS score of nausea was not statistically significant between three groups throughout the study ($P > 0.05$). Although seven patients (28%) in the first group (IV group) and four subjects in the second and third groups (16%) had nausea, the Chi-square test showed that the difference was not statistically significant. Three patients (12%) in Group 1, one subject (4%) in Group 2, and four patients (16%) in Group 3 had vomiting ($P = 0.19$). Two hours after leaving recovery room, none of the patients had nausea, as it is not in Table 2. The mean of systolic and diastolic blood pressure and the pattern of their change were not significantly different between groups.

Table 1: Patient's baseline and demographic data

Variable	Group 1 (*n*=25)	Group 2 (*n*=25)	Group 3 (*n*=25)	*P*
Age (years)	28.2±5.33	28.1±5.53	27±4.37	0.65
Weight (kg)	73.7±10.46	73.8±10.15	74±12.16	0.98
Baseline systolic blood pressure (mmHg)	110.4±12.06	113.6±12.87	115.2±9.73	0.34
Baseline diastolic blood pressure (mmHg)	68.8±8.57	72.2±9.36	71.2±9.71	0.41

Group 1: Patients received 50 μg fentanyl intravenously, Group 2: Patients received 50 μg fentanyl subcutaneously, Group 3: Patients received 50 μg fentanyl intranasally. Data are expressed as mean±SD. SD: Standard deviation

Table 2: Pain scores, systolic and diastolic blood pressure parameters measured during the study

Variable	Group 1 (*n*=25)	Group 2 (*n*=25)	Group 3 (*n*=25)	*P*
Pain VAS score				
In recovery room	7.6±1.1	6.6±2	6.8±2.1	0.037
After first 30 min	7.6±1.2	6.6±1.9	6.8±2	0.111
After second 30 min	7.5±1.3	6.8±1.4	7±1.8	0.280
After third 30 min	7.2±1.2	6.6±1.4	6.8±2	0.489
After fourth 30 min	6.6±1.1	6±1.6	6.4±1.9	0.379
After fifth 30 min	6.4±1.1	5.6±1.6	6±1.8	0.201
After sixth 30 min	5.9±1.2	4.8±1.5	5.6±1.95	0.035
After seventh 30 min	5.5±1.1	64.5±1.5	5±1.8	0.049
After eighth 30 min	5±1.2	3.8±1.5	4.4±1.6	0.016
Nausea VAS score				
In recovery room	1.4±2.7	1.2±2.9	1.2±3.3	0.964
After first 30 min	1.0±2.5	0.32±1.1	0.6±1.6	0.432
After second 30 min	1.0±2.5	0.4±1.3	1.2±2.9	0.471
After third 30 min	0.4±1.4	0	0.8±2.7	0.219
After fourth 30 min	0.4±2.0	0	0	0.373
Systolic blood pressure (mmHg)				
Before induction	110.4±12.06	113.6±12.87	115.2±9.73	0.337
Before fentanyl administration	101.8±9.77	108.4±11.43	107.4±14.93	0.128
5 min after fentanyl administration	104±9.89	108.6±11.5	108.8±6.17	0.135
15 min after fentanyl administration	104±9.89	108.6±11.5	108.8±6.17	0.135
30 min after fentanyl administration	104.4±10.34	108.6±11.5	108.8±6.17	0.196
Diastolic blood pressure (mmHg)				
Before induction	68.88.57	72.2±9.36	71.2±9.71	0.413
Before fentanyl administration	68.8±6.96	70±9.12	67±8.30	0.512
5 min after fentanyl administration	64.2±7.02	69±9.12	67.2±7.91	0.112
15 min after fentanyl administration	64.2±7.02	69±9.12	67.2±7.91	0.112
30 min after fentanyl administration	64.2±7.02	69±9.12	67.2±7.91	0.112

Group 1: Patients received 50 μg fentanyl intravenously, Group 2: Patients received 50 μg fentanyl subcutaneously, Group 3: Patients received 50 μg fentanyl intranasally. Data are expressed as mean±SD. SD: Standard deviation, VAS: Visual analogue scale

DISCUSSION

The purpose of this study was to evaluate the effect of using IV, subcutaneous and INF for pain management in patients undergoing cesarean section.

The lack of a major difference between groups in the reduction of self-reported pain intensity during the first 3 h after surgery makes sense because it takes times to reach effective blood fentanyl concentrations. However, a significant group difference at 4 h after application of the fentanyl was achieved and individuals who received subcutaneous fentanyl had consistently lower self-reported pain intensity scores than the other groups without any side effect. These findings are of clinical significance.

Fentanyl, a synthetic opioid, is 7000 times more lipophilic and 75–200 times more potent, than morphine.[13] It is highly protein bound and has a high affinity for fat therefore extended exposure may consequence in accumulation in fat tissues.[14] The drug has entered palliative care as a useful strong opioid,[11] and is efficacious, well accepted, and well tolerated by patients than morphine in some cases.[15,16] The onset

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of action of fentanyl is almost immediate when the drug is given intravenously. However, the maximal analgesic effect may not be noted for several minutes. The usual duration of action of analgesic effect is 30–60 min after a single IV dose of up to 100 μg. IVF is used safely for severe cancer pain when the rapid titration is being considered.[17] Transmucosal fentanyl has been used in cancer pain management as an alternative route for opioid administration or as rotation strategy.[18,19] INF has become available, providing an alternative analgesic that does not rely on venous access. The IN delivery of fentanyl provides rapid absorption (therapeutic levels within 2 min) and provide significant reduction in pain scores by 5 min. It has duration of action of at least 30 min and excellent bioavailability (at least 50%).

Borland showed that INF is a suitable analgesic agent for use in pediatric burns dressing changes either by itself or in combination with oral morphine as a top-up titratable agent.[20] Similarly, Finn *et al*.'s study revealed that patient controlled INF was similar in efficacy and safety to oral morphine for relief of procedural burns wound care pain.[21] Davies reported that fentanyl pectin nasal spray provided superior and more rapid pain relief with greater acceptability from breakthrough cancer pain (BTCP) compared with immediate-release morphine sulfate in patients with one to four BTCP episodes/day while receiving ≥60 mg/day oral morphine (or equivalent) for background pain.[16]

Christrup *et al*. compared the tolerability, pharmacokinetic profile, and the efficacy of IN and IV administration of fentanyl in acute, episodic pain in patients undergoing third molar extraction. He concluded that the onsets and durations of analgesia were not significantly different between single doses of INF and IVF, and both routes of administration were generally well tolerated.[10] Since the IV administration causes quick systemic penetration, the finding that the clearance with these two routes was similar suggests that bioavailability via the IV route is high.

Moreover, data on the pharmacokinetics of subcutaneous fentanyl does not exist in healthy volunteers. Capper studied pharmacokinetics of fentanyl after subcutaneous administration in volunteers. He reported that absorption of subcutaneous fentanyl was relatively rapid and similar to the rate of absorption previously reported for subcutaneous morphine; the terminal half-life for fentanyl was substantially longer (10 h) than that of morphine (2.1 h), and blood concentrations were no more variable than that after administration by other non-IV routes.[22] Watanabe *et al*. studied retrospectively and showed that fentanyl by continuous subcutaneous infusion is a useful alternative for cancer pain.[23] It is revealed that subcutaneously administered medicines are absorbed primarily by capillary diffusion, which makes it possible to avoid the so-called first-pass effect and therefore, there are no significant differences between the subcutaneous and IV application of medicines in terms of their absorption, efficacy and the frequency of side effects[24] which can explain the findings of our study.

Limitations

However, it is not yet clear whether the concentration-effect relationship elucidated here applies to patients with different types of pain. Furthermore, the patients involved in this study were relatively young; therefore, prediction of the pharmacokinetics and pharmacodynamics of IN and subcutaneous fentanyl in older patients remains to be determined. Also, more emphasis should be placed on several concepts to obtain maximal efficacy when using IN medications. These concepts are minimizing drug volume while maximizing drug concentration, adequate dosing to overcome bioavailability limitations presented by the nasal mucosa, utilization of both nostrils to double the available mucosal surface for absorption and medication delivery characteristics.

CONCLUSIONS

The IN and IV routes of fentanyl administration are similar regarding to their pain control and side effect incidence. Subcutaneous fentanyl is an effective alternative to IV and IN routes of administration for pain management particularly for patients where cannulation is undesirable or impossible.

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Conflicts of interest

There are no conflicts of interest.

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