Determining the optimal fentanyl dose for dilation and curettage procedures

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Summary

Aim: This study attempted to determine an optimal dose of fentanyl, a drug frequently used in dilation and curettage (D&C) procedures, which is commonly performed as a brief outpatient intervention. *Methods:* The optimal fentanyl dose was determined using Dixon's up-and-down method. The study was accomplished with a beginning fentanyl dose of 1 μg kg^{-1} with a step size of 0.1 μg kg^{-1} fentanyl. *Results:* The ED50 [95% confidence interval (CI)] for fentanyl for successful anesthesia in D&C procedures was found to be 0.45 (0.35-0.55) μg kg^{-1} and the ED95 value was 0.50 (0.45-0.60) μg kg^{-1}. *Conclusion:* This dose is considerably lower than the standard dose that is used at present, which is 1 μg kg^{-1}. To the best of our knowledge, the current study is the first to show that a significantly reduced dose of fentanyl can be as effective as higher doses in D&C procedures using Dixon's up-and-down method.

Key words: Fentanyl; Dilation and curettage; Optimal dose.

Introduction

Dilation and curettage (D&C) is one of the most frequently performed gynecological procedures and one that is both brief in duration and undertaken as an outpatient procedure. A dose of 1 μg kg^{-1} fentanyl is commonly used as an analgesic in D&C [1] to alleviate significant pain that is likely to be involved in the procedure [2, 3].

While a fentanyl dose of 1 μg kg^{-1} is frequently used for this procedure, to the best of our knowledge there is no study in the literature that has used Dixon's up-and-down method to determine the optimal dose of fentanyl for D&C [4].

The aim of this study was to determine the optimal dose of fentanyl, a drug frequently used in D&C procedures, using Dixon's up-and-down method.

Material and Methods

The study was conducted at the Adnan Menderes University Hospital. Patients wishing to participate in the study completed a written informed consent.

Patients who met the inclusion criteria and who were about to undergo a D&C procedure were included in the study. The research was carried out with a total of 30 patients.

Patients between the ages of 18-60 assessed as I or II in the physical status classification of the American Society of Anesthesiologists (ASA) were enrolled in the study. Patients requiring intubation of the trachea or the use of a laryngeal mask, pregnant patients, patients who had reactive airway disease or a body mass index of > 35 kg/m^2, those with liver, kidney or lung disease, neuromuscular disease, as well as other patients who were to undergo the procedure as an emergency intervention were excluded from the study.

The patients were placed on an overnight fast and premedication was not administered. In the operating room, an intravenous (IV) cannula was first secured to the dorsum of the patient's hand and an infusion of lactated Ringer's solution was initiated. All patients in the operating theater were subjected to standard monitorization with a five-lead ECG noninvasive blood pressure and pulse oximetry.

The first patient was given an IV bolus dose of fentanyl 1 μg kg^{-1} (Fentanyl citrate, USP 50 mcg/ml; Abbot Laboratories, Chicago, IL). New fentanyl doses were determined using Dixon's up-and-down method according to the response received on the previous test doses. A step size of 0.1 μg kg^{-1} was used for fentanyl in the study. An effort was made to determine the optimal fentanyl dose using Dixon's up-and-down method, which has been used in many other previous studies to determine optimal dosage of various medications used in anesthesiology. If successful anesthesia could not be attained in the D&C procedure, the next patient was administered a fentanyl dose increased by 0.1 μg kg^{-1}. If the procedure was successfully performed, the next patient's fentanyl dose was reduced by 0.1 μg kg^{-1}.

A successful D&C procedure was defined as absence of recurring movement during the procedure and serious increase or decrease in hemodynamic signs; also, the non-presence of side effects of fentanyl such as dose-related respiratory depression.

The patient was administered 3-min preoxygenation prior to the induction of anesthesia. Following the fentanyl infusion, the patient's basal measurements were taken. Later, lidocaine (Jetocaine simlex ampule; Adeka Pharmaceutical, Istanbul, Turkey) IV 1 mg/kg was administered. Anesthesia induction was achieved in the patients with propofol (Propofol 1% Fresenius, Fresenius Kabi, Australia GmbH), and sustained with a facemask with 60% nitrous oxide (N2O) in oxygen with a fresh gas flow of 4 l/min^{-1}. Blood pressure, heart rate and oxygen saturation were recorded during the procedure. Clinically significant hypotension and bradycardia were defined as a reduction of mean arterial pressure and heart rate by > 30% compared to the basal measurement during the induction of anesthesia. The procedure ended when the gynecologist pronounced the intervention completed.

Statistical analysis

Statistical analysis for the study was carried out with the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL,

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Table 1. — *Patient characteristics*.

Age (years)	38.9 ± 10.3
Weight (kg)	67.6 ± 10.6
Height (cm)	160.7 ± 8.56
Anesthesia time (min)	9.2 ± 0.88
ASA physical status I/II (n)	14/16
Duration of surgery (min)	7.47 ± 1.14

Table 2. — *The 50% effective dose (ED50) and 95% effective dose (ED95) of fentanyl*.

ED50	ED95
0.45 (0.35-0.55) μg kg^{-1}	0.50 (0.45-0.60) μg kg^{-1}

USA), Version 14.0; p values < 0.05 were considered significant.

Data is expressed as mean ± standard deviation (SD). The study attempted to determine the optimal fentanyl dose using Dixon's up-and-down method.

The analysis of the values for a 50% effective dose (ED50) were based on the calculation of the mid-point concentration of all independent pairs of patients displaying a crossover concentration. The ED50 was accepted as the average of the crossover midpoints in each pair. A probit test was also used for the up-and-down sequences and making the calculation of a mean fentanyl dose possible with a confidence interval (CI) of 95%.

A probit test that offered the best-fitting sigmoid curve was used to determine the maximal likelihood estimators of the model variables.

Results

A total of 30 patients participated in the study. Characteristics of the subjects are shown in Table 1.

The ED50 (95% CI) for fentanyl, obtained with probit analysis, found for successful anesthesia in D&C procedures was 0.45 (0.35-0.55) μg kg^{-1} and the ED95 value for fentanyl was 0.50 (0.45-0.60) μg kg^{-1} (Table 2).

Discussion

One of the most common outpatient operations performed in the obstetrics and gynecology branch of medicine is the D&C procedure. Significant pain is an expected outcome of this surgery. The reason for the pain is generally related to cervical dilation and tissue extraction required during the procedure [5]. An important consideration in the operation is the patient's movement in response to pain. Because sharp tools, curettes, are used in the operation, patient movement during the procedure may lead to uterine rupture. Movement may also cause injuries of the intraabdominal organs such as the intestines and urinary tract [6]. This potential danger is an important factor to consider in terms of its significant potential for morbidity and even mortality. It is of great importance in terms of patient comfort, to ensure that she feels no pain during the procedure [7].

Opioids are the choice analgesic drugs in D&C. One of the opioids that is most commonly used because of the various advantages it offers is fentanyl. Fentanyl is a synthetic opioid. Fentanyl specifically interacts with the opioid μ receptor and is somewhat effective on δ and κ-opioid receptors [8]. Fentanyl's cost advantage and its fast-acting effects give the molecule an edge over many other opioids [9]. At the same time, availability of fentanyl in suitable preparations other than in IV form contributes to making it a drug that is used effectively and successfully today [10-12].

Although fentanyl is frequently used in D&C procedures, to the best of our knowledge, the literature contains no reference of any research that has used Dixon's up-and-down method to determine an optimal dose of fentanyl for D&C.

An analysis was performed to find the ED50 value (95% CI) for fentanyl for successful anesthesia in D&C procedures. This study is significant in that, it is the first study to use Dixon's up-and-down method to show that fentanyl can be just as effective in markedly reduced doses in D&C procedures.

Fentanyl is commonly used as an analgesic in brief gynecological surgery and the practical, non-evidence-based dose that is generally administered is 1 μg kg^{-1} [1]. In a study we carried out previously, it was found that fentanyl was effective in smaller doses of up to even 0.5 μg kg^{-1} [13]. We found that smaller doses not only achieved analgesia but side effects were reduced as well. Moreover, the added advantage of faster recovery times in the group studied contributed to the conclusion that small doses of fentanyl could be as effective as higher doses for outpatient surgery.

The use of Dixon's up-and-down method was one of the strengths of our study. Dixon's up-and-down method has been frequently and successfully used to determine optimal dose studies [14-16]. While conventional techniques of determining doses call for numerous subjects, Dixon's up-and-down method significantly reduces the number of cases needed to make the determination. While reducing the number of subjects needed in a study, Dixon's up-and-down method still provides the opportunity to obtain similarly successful outcomes that can serve to determine optimal dosage.

There were some limitations to the study. One was the issue of blinding. The anesthesiologist participating in the study could not be blinded to the fentanyl dose. On the other hand, he was unaware of the basic purpose of the study. At the same time, the person evaluating the study and giving the instructions to increase or decrease the dose of the drug was an independent analyst who was blinded to the fentanyl dose. From this perspective, we believe that the study did achieve blinding to a significant extent.

Up-and-down methods are based on a simple sequential design that is used to define the dose at the 50^{th} quantile (ED50), reducing the total number of subjects needed for the computation.

Because of the interest of anesthesiologists in the ED95, this is often calculated using the isotonic regression estimator with the CIs derived by bootstrap sampling. Despite the fact that isotonic regression provides a

backup analysis for determining ED50 with a smaller bias and tighter CIs as compared to standard probit or logit regression, which usually produce biased estimators [16, 17], extrapolating ED95 from small up-and-down data may fail to yield an exact calculation.

Another limitation of the study was defining successful anesthesia for the D&C procedure when a facemask is being used. We defined successful anesthesia in this case as the absence of recurring movement during the procedure, no serious increase or decrease in hemodynamic data, and the non-presence of dose-related side effects of fentanyl such as respiratory depression [18].

A recommendation might be to have future studies explore the duration of time in the operating room and in post anesthesia care unit when the ED50 or ED95 of fentanyl determined in the present study are administered, as well as to review the status of patients in terms of early discharge from the hospital. In taking a brief and global look into the practical application of significantly reducing the opioid dosage to the levels determined in the present study, and with the consideration that this procedure is a very common surgical intervention, another worthwhile study would be to compare costs for this dose with the costs of conventional 1 μg kg^{-1} doses of fentanyl [19].

In conclusion, the use of Dixon's up-and-down method to determine an optimal fentanyl dose for successful D&C procedures yielded the results that the ED50 (95% CI) value for fentanyl for successful anesthesia in D&C procedures was 0.45 (0.35-0.55) μg kg^{-1} and the ED95 value was 0.50 (0.45-0.60) μg kg^{-1}, a significantly lower dose than the standard dose currently administered.

The study is significant in that it is the first study, to the best of our knowledge, that has used Dixon's up-and-down method to show that significantly reducing fentanyl doses in D&C procedures may produce the same effect as the currently accepted standard dose of 1 μg kg^{-1}.

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