A Prospective Randomized Controlled Trial of Two Different Sedation Sequences for Third Molar Removal in Adults

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Purpose: In oral and maxillofacial outpatient surgery, sedation techniques are an important component in patient management for a wide variety of surgical procedures. Fentanyl and midazolam are commonly used sedatives with different mechanisms of action and specific analgesic or amnestic properties. This study examined whether the order of their administration would affect a patient's pain perception or procedural vital signs.

Materials and Methods: After institutional review board approval and written informed consent, a prospective, randomized, parallel-group clinical trial was conducted in patients who planned to undergo removal of at least 2 third molars under intravenous moderate sedation. Patients were randomly assigned to 1 of 2 groups. The fentanyl-first group received fentanyl and then midazolam; the midazolam-first group received midazolam and then fentanyl. Recollection of the intraoperative pain score was assessed 24 hours after surgery using the Wong-Baker FACES pain scale. The Mann-Whitney *U* test was used to assess for the presence of a statistically significant difference between the 2 groups. Statistically significant differences in procedural vital sign fluctuations were examined using the *t* test. Patients' satisfaction with the procedure was assessed and intergroup comparisons were made.

Results: Sixty-six patients were enrolled, 1 of whom did not complete the study. Recollected procedural pain scores at 24 hours after surgery were not statistically different between groups. Median scores on the Wong-Baker FACES pain scale for the 2 groups were 2.0 (interquartile range, 3.1) for the fentanyl-first group and 1.5 (interquartile range, 2.5) for the midazolam-first group ($P = .333$). There was no statistical difference in the change in vital signs from baseline to 2 surgical end points in the 2 groups. In addition, patient satisfaction with the procedure did not statistically differ between the 2 groups.

Conclusions: In this study, selective sequencing of midazolam or fentanyl during an intravenous moderate-sedation procedure did not result in a measurable difference of recollected procedural pain scores at 24 hours after third molar extraction. The choice of the sedation agents and the order of their

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administration should be tailored to the patient's needs, type of surgical procedure, and surgeon preference.

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Sedation is a vital component of patient management for a wide variety of surgical procedures in oral and maxillofacial surgery (OMS) outpatient practices. The choice of sedation technique is made according to the patient's needs and health status, type of surgical procedure to be performed, and surgeon preference.

The ideal sedation agent used in outpatient practices should provide a rapid onset of action and stable operating conditions, it should be easily reversed, it should ensure a fast and a predictable recovery, and it should carry very few side effects.[1] Midazolam (a benzodiazepine) and fentanyl (an opioid) are 2 sedation agents that satisfy these requirements; therefore, they are 2 of the most commonly used drugs for intravenous moderate sedation in outpatient OMS practices.[2] Surgeons in the Department of OMS at Tufts University (Boston, MA) use midazolam or the combination of midazolam and fentanyl for most of their intravenous moderate-sedation procedures.

The efficacy and safety of midazolam, fentanyl, and their combination in outpatient intravenous moderate sedations have been well established in the literature.[3-15] The choice of the order in which these medications are administered is left primarily up to the practitioners' preference; the effect of the order in which these medications are administered on patient outcomes has not been scientifically studied. Although every patient encounter should be individualized and there is not one universal technique that will be suitable for all patients, the authors approached this issue with a fixed-dose study protocol to determine whether the difference in the order of administration of these medications in healthy patients for routine OMS procedures would produce clinically important results.[16]

This study examined the effect of the order in which intravenous midazolam and fentanyl are administered during an outpatient OMS procedure (ie, fentanyl and then midazolam and vice versa) on patient outcomes.

To explore patient outcomes related to the alteration of the order in which intravenous sedation medications are administered, a double-blinded, randomized, clinical trial of patients undergoing outpatient surgical removal of third molars was conducted. The primary endpoint of this study was the recollection of intraoperative pain. In addition, the authors explored the effect of the alteration of the sequence of the order in which intravenous medications are administered on intraoperative vital signs. This was an exploratory study aimed at gathering preliminary data. The results from this study will be the first documentation of the effect of altering the sequence of administration of intravenous sedation medications on intraoperative pain perception.

The purposes of this study were to:

1. explore the effect of the order in which intravenous sedation medications are administered (midazolam and fentanyl) on intraoperative pain perception
2. compare the effect of the order in which intravenous sedation medications are administered on patient satisfaction with the sedation procedure
3. compare the effect of the order in which intravenous sedation medications are administered on clinical outcomes (including fluctuations of vital signs)

Materials and Methods

A prospective, randomized, parallel-group clinical trial was conducted in 66 patients who planned to undergo removal of at least 2 third molars under intravenous moderate sedation at the Department of OMS at the Tufts University School of Dental Medicine. The study was approved by the institutional review board and is in accordance with the Declaration of Helsinki.

Potential subjects underwent a screening process at which point an informed consent was obtained. The surgeons explained to the participants the proposed surgical procedure, risks and benefits of the procedure, and the study protocol. Routine physical and radiographic examinations were completed. All patients had to meet the inclusion criteria listed in Table 1. Patients who requested general anesthesia or a deeper level of sedation were excluded (according to the exclusion criteria listed in Table 1).

Recruited patients were consecutively assigned a participant number (from 1 through 66) and were scheduled for their surgical procedure. A computer-generated randomization scheme was produced assigning numbers 1 through 66 into 2 groups. The fentanyl-first group would receive fentanyl first in the sedation sequence, and the midazolam-first group would receive midazolam first in the sedation sequence. The key connecting the patient number with the assigned group was locked at the principal investigator's office and was accessed by the surgeons immediately before commencing the surgical