A Comparison of Dexmedetomidine Versus Propofol for Use in Intravenous Sedation

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BACKGROUND/SIGNIFICANCE

Intravenous sedation (IVS) is an integral aspect of the oral and maxillofacial surgeon's practice. For many minor oral surgical procedures, intravenous sedation is often necessary to manage patient anxiety and discomfort, while also facilitating a safe and efficient procedure in the outpatient setting. Ideally, sedative agents have anxiolytic, amnestic, and analgesic properties while maintaining cardiopulmonary stability. The medications used should allow for rapid onset of action, as well as a quick recovery, with minimal side effects.

Several pharmacologic agents are frequently used for conscious sedation in the oral surgery practice. These medications often include midazolam, fentanyl, ketamine and propofol, either alone or in conjunction with one another. While propofol and fentanyl have proved to be efficacious agents for use in intravenous sedation, they are not without associated side effects. Propofol has the potential to cause a quick progression from conscious sedation to general anesthesia, with the undesired effect of associated cardiovascular and respiratory depression.[1,2] Decreased respiratory drive, hypotension, and dose-dependent bradycardia are often seen with opioid analgesics such as fentanyl.[1,2] Ketamine can cause emergence delirium, increased salivation and pulmonary secretions, tachycardia, and post-operative nausea and vomiting (PONV).[3]

Midazolam is a benzodiazepine that is an attractive agent for intravenous sedation due to its sedative, amnestic, and hypnotic properties. In addition, it is associated with very minimal cardiovascular and respiratory changes.[4,5] However, midazolam lacks significant analgesic effects, and therefore is routinely used in conjunction with additional agents when used for procedural sedation. Though several studies have explored the use of midazolam as a sole anesthetic, very high doses are required for deep sedation. This can lead to dose-dependent respiratory depression, prolonged emergence and longer recovery time.[4,6]

Dexmedetomidine (Precedex, Hospira, Inc., Lake Forest, IL) is a highly selective alpha2-adrenergic agonist that possesses hypnotic, sedative, anxiolytic, and analgesic properties.[1,5,7-9] It is currently approved for use as a sedative agent in ICU patients, and has been proven a safe and effective agent for use during procedural sedation.[1,6,9,10] In the central nervous system, the primary site of action of dexmedetomidine is the locus ceruleus, resulting in a level of sedation similar to natural sleep, associated with fast and easy arousal.[7,11,12] It demonstrates relative hemodynamic stability with little effect on respiratory depression.[1,5] Unlike propofol and fentanyl, dexmedetomidine's lack of adverse effects on respiration makes it an attractive agent for use during intravenous sedation in the oral and maxillofacial surgery practice.

Several studies involving dexmedetomidine exist in the oral and maxillofacial surgery literature. Dexmedetomidine has been compared as a substitute for midazolam, as well as propofol, in conscious sedation by several authors. For third molar surgery, dexmedetomidine was noted to preserve the respiratory rate and oxygen saturation throughout operation and recovery periods.[4] Fan et al also found no significant differences in respiratory rate when comparing the two agents for conscious sedation.[5] In comparison to midazolam, Ryu et al reported safe sedation without airway compromise and minimal effects on the respiratory system.[13]

Dexmedetomidine also possesses sympatholytic properties, and is commonly associated with a dose-dependent decrease in both heart rate and blood pressure.[4,9] Taniyama et al compared dexmedetomidine

to propofol for intravenous sedation for minor oral surgical procedures. They found that dexmedetomidine lead to significant hemodynamic changes during the initial loading infusion.[14] An initial increase in blood pressure was seen, followed by a significant decrease in both systolic and diastolic blood pressure, as well as heart rate. These variations are attributed to the fact that dexmedetomidine does not have selectivity for alpha-2A versus alpha-2B receptors.[14] While alpha-2A receptors are found in the CNS and are therefore responsible for the analgesic and sedative effects of the drug, alpha-2B receptors are found in vascular smooth muscle and thereby mediate the hypertensive effects of high doses of dexmedetomidine. Because of this, initial loading doses of dexmedetomidine may be associated with a transient increase in blood pressure, followed by an overall reduction in blood pressure and heart rate from baseline.[4,12,15] Hall et al reported that dexmedetomidine demonstrated a decrease in heart rate from baseline between 16 and 18%, and a decrease in blood pressure of 10 to 20%.[15] However, in some studies, similar biphasic changes were not observed, possibly due to the use of a lower dosage of dexmedetomidine.[4]

Aside from dose-dependent depression of the cardiovascular system, dexmedetomidine has been associated with minimal to no amnesic effects.[4] One other possible disadvantage of dexmedetomidine as a sedative agent for in-office procedures is the increased postoperative recovery time.[6] Peak sedative effects of the drug occur approximately 90-105 minutes after administration, continuing to as much as 180 minutes.[13] This may necessitate post-operative observation periods of increased duration. Intravenously administered dexmedetomidine has a distribution half-life of 6 minutes and an elimination half-life of 2 hours.[12] It undergoes biotransformation in the liver and is excreted primarily in the urine.[9]

PURPOSE

The primary goal of this prospective randomized trial is to determine whether there is a significant difference in the number of respiratory events requiring intervention during the intravenous deep sedation/general anesthesia (DS/GA) between two different anesthetic medication combinations: midazolam and dexmedetomidine versus midazolam, fentanyl, and propofol.

Secondary variables to be measured include hemodynamic changes during the sedation, difference in the amount of movement during injection of local anesthesia, time until discharge, patient satisfaction with the sedation, and surgeon satisfaction with the sedation.

HYPOTHESIS

A sedative combination of midazolam with dexmedetomidine for intravenous DS/GA during third molar surgery will provide less respiratory events requiring intervention when compared to a sedative combination of midazolam, fentanyl, and propofol.

STUDY DESIGN

The proposed study is a prospective, randomized, controlled trial, with two intravenous treatment groups during third molar surgery. The patient will be masked to the anesthetic protocol used during the IVS for third molar surgery, and there will be a masked independent scorer to evaluate the number of respiratory events requiring intervention during sedation, extent of patient movements, facial expressions and vocalization during local anesthesia injection, and time of procedure, time to ambulation, and time of virtual discharge.

Group 1 (Control): Midazolam/fentanyl/propofol (MFP)

Group 2 (Study): Dexmedetomidine/midazolam (D/M)

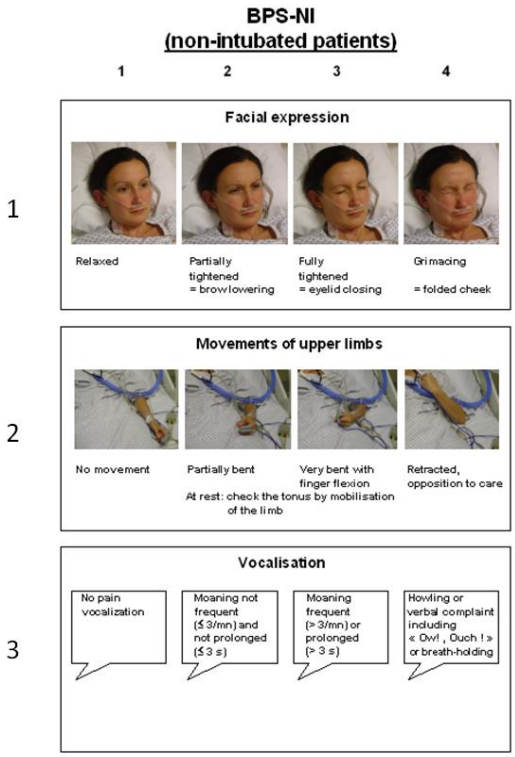
Primary Outcomes

1. To compare the groups regarding the number of respiratory events requiring intervention, described as:
    a. Chin lift/jaw thrust
    b. Tongue trust
    c. Yankauer suctioning
    d. Positive pressure O2
    e. Placement of an oral or nasal airway

Secondary Outcomes

1. To compare the groups regarding movement of the patient during the first injection of local anesthesia during the IVS at time of injection measured using the Scorer Assessment Form (Appendix A), which includes:
    a. The Behavioral Pain Scale – Non-Intubated patients (BPS-NI) (Figure 1)
    b. Cooperation Scale (Figure 2) at 5 and 15 minutes

Figure 1. BPS-NI Scale



1+2+3 = Total BPS Value
From 3 (no pain) to 12 (maximum pain)

2. To compare patient satisfaction of treatment using D/M versus MFP combinations
    a. Patient Satisfaction Survey: VAS; measuring overall satisfaction with the IVS and memory of procedure (Appendix B)

3. To compare the surgeon satisfaction of the IVS using D/M versus MFP combinations
    a. Surgeon Satisfaction Survey (Appendix C)
    b. Cooperation Scale (Figure 2)

Figure 2. Cooperation Scale

Table 1. COOPERATION SCALE[9]

Did the patient's movements during the local anesthesia or the extractions interfere or delay treatment?
- 0..... No interfering movements
- 1..... Minor movements, positioning remained appropriate
- 2..... Minor movements, patient had to be repositioned
- 3..... Movements grossly interfered with the procedure

To what extend did the patient verbalize discomfort during the procedure?
- 0..... Not at all
- 1..... Some verbalization, but did not indicate pain or discomfort
- 2..... Some verbalization indicating pain or discomfort
- 3..... Complained frequently during the procedure

Did the patient show nonverbal signs of discomfort during the procedure?
- 0..... Not at all
- 1..... Slight discomfort, occasional grimaces
- 2..... Moderate discomfort, feet/hands tensed, tears in eyes
- 3..... Marked discomfort apparent during procedure

Total COOPERATION SCORE (out of 9): _____

4. To compare the differences in hemodynamic stability using a D/M combination compared to the MFP combination. (In this study, a deviation from baseline of both the blood pressure and heart rate by 20% or greater will be considered clinically significant)
   a. Change in heart rate (change ≥ 20 BPM)
   b. Change in blood pressure (NIBP) (change ≥ 20%)

5. To assess whether a D/M combination leads to a significant change in respiratory depression compared to the MFP combination.
   a. Change in respiratory rate (change ≥ 20%)
   b. Change in arterial oxygen saturation (as measured by pulse oximeter)
      i. number of events of ≤92%

6. To assess whether a D/M combination increases postoperative recovery time when compared the MFP combination.
   a. Duration of procedure
   b. Time to ambulation (to recovery room)
   c. Time to "virtual discharge" (comparative statistic)
      i. Aldrete score of ≥ 9 or pre-procedure score is met (Figure 3)
      ii. All subjects are required to stay a minimum of 30 minutes after the end of the procedure. Therefore, at least two postoperative vital sign readings will be obtained. If the subject meets discharge criteria prior to 30 minutes, this time will be the "virtual discharge" time.

Figure 3. Aldrete Score

Parameter	Description of patient	Score
Activity level	Moves all extremities voluntarily/on command	2
	Moves 2 extremities	1
	Cannot move extremities	0
Respirations	Breathes deeply and coughs freely	2
	Is dyspneic, with shallow, limited breathing	1
	Is apneic	0
Circulation (blood pressure)	Is 20 mm Hg > preanesthetic level	2
	Is 20 to 50 mm Hg > preanesthetic level	1
	Is 50 mm Hg > preanesthetic level	0
Consciousness	Is fully awake	2
	Is arousable on calling	1
	Is not responding	0
Oxygen saturation as determined by pulse oximetry	Has level >90% when breathing room air	2
	Requires supplemental oxygen to maintain level >90%	1
	Has level <90% with oxygen supplementation	0

Maximum total score is 10; a score of ≥9 is required for discharge.

Randomization

Subjects will be assigned to D/M or MFP by a computer-generated randomization scheme with an undisclosed blocking factor in accordance with a 1:1 randomization ratio. A packet of sealed envelopes containing the randomization code and study ID will be provided to the anesthetist investigator who will be instructed to open the next envelope in sequence to determine the sedation the patient is to receive. He or she will record the patient's name on the sheet of paper and file it in the patient's chart. The patient's data will be de-identified by affixing the patient's study ID on all subsequent data files and forms associated with the patient for this trial.

Investigator Team Roles

Surgeon: Responsible for performing the surgery (masking is near impossible given that dexmedetomidine is colorless whereas propofol is white). Furthermore, in the outpatient OMFS surgery clinic the patient's airway is not secured with an endotracheal tube. Masking the surgeon may be unsafe in this setting and thus will not be attempted.

Anesthetist: Responsible for medication preparation and administration, recording of drug administration and vital signs, patient monitoring, monitoring of apneic events. The anesthetist will be unmasked by necessity and will not evaluate outcomes.

Scorer: Responsible for recording and scoring the respiratory events requiring intervention, BPS-NI Scale, length of procedure, time to discharge, any adverse events or outcomes, and vital signs; scorer will be masked as to treatment group.

Blinding

Only the scorer will be masked. To preserve masking of the scorer, all medications, infusion pump, and IV tubing will be located behind a barrier to ensure that the scorer will not know the group to which the patient has been assigned. In addition, the patient will not be informed as to their sedation, thus minimizing bias in determining patient satisfaction with treatment.

METHODS

1. Procedures to evaluate inclusion/exclusion
    a. Past medical history, medications, allergies
    b. Clinical examination
    c. Every patient will have a panoramic radiograph and a cone beam CT if required based on surgeon's examination
2. Informed consent followed by opening envelope to derive randomization group
3. Procedures performed as part of the trial.
    a. NPO status performed by the anesthetist
    b. Standard ASA monitors including pulse oximetry, NIBP, three-lead EKG, capnography
    c. Pre-treatment vitals and BMI recorded by the anesthetist
    d. IV access obtained by the anesthetist or surgeon
    e. Administration of antibiotic and dexamethasone
        i. The subject will preoperatively be administered 600mg of clindamycin intravenously, unless the patient has a reported allergy, in which case an alternative antibiotic will be given. In addition to the antibiotic, 8mg of dexamethasone will be given intravenously to aid in reducing postoperative edema.
    f. Supplemental oxygen will be provided via nasal cannula at 2 L/min
    g. Vital signs will be recorded every 5 minutes by scorer
    h. The scorer will document respiratory events requiring intervention (i.e. chin lift, positive pressure). Required cessation of infusion or additional requested boluses will also be recorded.
    i. Anesthetist begins IVS
        i. Group 1 (control):

1. 0.03mg/kg midazolam, 0.1 mcg/kg of fentanyl and an infusion of propofol at 125 mcg/kg/min

2. Propofol boluses at 0.1 mg/kg

ii. Group 2 (study):

1. 0.03mg/kg midazolam, initial bolus of dexmedetomidine at 1 mcg/kg for 10 minutes followed by a maintenance infusion of 0.5 mcg/kg/hr

2. All medications, along with the infusion pump and IV tubing, will be located behind a barrier so that the scorer will not know which medications are

j. Local anesthetic administration (2% lidocaine with 1:100,000 epinephrine)

k. Operative procedure

l. Anesthetic will be discontinued at initiation of suturing/closure

m. The procedure completion time will be recorded by the scorer as the time at which the surgeon puts down the last instrument.

n. Vitals will be obtained at the conclusion of the procedure and every 15 minutes thereafter until discharge. Two sets of post op vital signs will be evaluated statistically for each patient (15 and 30 minutes).

o. The patient will be discharged based on the criteria found on the modified Aldrete score (greater or equal to 9 or the preoperative score is met).

4. Evaluations

a. The surgeon will complete a Surgeon Satisfaction Survey regarding satisfaction with the IVS and the Cooperation Scale.

b. The patient will complete the Patient Satisfaction Survey

<u>Stopping Criteria</u>

IVS will be stopped intraoperatively in this study as it would in the regular clinic setting. If the procedure cannot be completed safely due to inability to control the patient from moving with the sedative agents, the procedure and sedation will be discontinued. Other criteria to stop the IVS will include tachycardia >150bpm, bradycardia <40bpm, and/or inability to control the patient's airway.

IV medications will be temporarily stopped if a patient remains apneic or in laryngospasm after intervention. The IV medication can be resumed later in the procedure.

Patient Sample

Inclusion Criteria

- Age 18-35 with the ability to sign informed consent
- Subject must have 3-4 partial or full bony impacted third molars requiring surgical extraction
- ASA Class I or II
- English-speaking and Spanish-speaking subjects

Exclusion Criteria

- ASA Class III or higher
- Patients taking alpha-2 agonists or benzodiazepines
- Allergy or drug reaction to any of the drugs used in this study (benzodiazepines, opioids, propofol, alpha-2 agonists, NSAIDs, local anesthetic)
- BMI greater than 30
- History of or current substance abuse or alcoholism
- History of mood-altering medications, tranquilizers, or antidepressants.
- Pregnant females

Information Obtained

As with any medical evaluation, the subject's DOB, medical record number (MRN), full medical history, and history of present illness will be obtained.

No human specimen or samples will be obtained.

Risks

Subjects in the study group are not at increased risk compared to the control group.

Normal risks associated with third molar surgery will be discussed at your initial visit. These include, but are not limited to, pain, bleeding, infection, swelling, damage to adjacent teeth/structures, temporary or permanent numbness of the lower lip/chin/cheek/gums/teeth and/or tongue, chronic sinusitis, oroantral communication, alveolar osteitis (dry socket), and the need for additional procedures.

Risks associated with deep sedation/general anesthesia include, but are not limited to, headache, nausea, vomiting, allergic reaction, cardiac depression or arrest, respiratory depression or arrest, loss of protective reflexes including the ability to maintain an airway independently or respond to verbal commands or physical stimulation, aspiration, laryngospasm, bronchospasm, syncope, seizure, neurological impairment, or prolonged recovery from anesthesia.

Benefits

Subjects in the study group have no increased benefit over the control group.

The benefit of removing third molars are to remove source of infection and pain, decreased chance of future infection, and decreased chance of future pathology.

Data Safety Monitoring Plan

Data will only be saved on one computer (password protected) at the Blondell Dental Clinic at Montefiore Medical Park in the primary investigator's office (Dr. Patrick Nolan). The subjects are assumed to present randomly and are assigned study numbers in sequence according to the exterior envelope label. These study IDs are not associated with any personal identifiers with the following exceptions: 1) The patient's name and MRN will be recorded on the envelope (the envelope will be shredded at the end of the procedure), and 2) The study ID-medical record key will be saved in a separate database with a different password. The questionnaire documents will be locked in a filing cabinet in the primary investigator's office until the conclusion of the study when they will be shredded. In addition, safety findings will be provided to an independent statistician after 25%, 50%, and 75% of the patients have been followed for 6 weeks or longer.

Consent forms and research records will be scanned into the subject's electronic dental record. All other documentation will be shredded at the conclusion of the study.

Data Safety Monitoring Committee

1. Jason Baker, DMD
   Attending surgeon, Montefiore Medical Center
   Clinical Instructor, Albert Einstein College of Medicine

2. Mauricio Wiltz, DDS
   Attending surgeon, Montefiore Medical Center
   Assistant Professor, Albert Einstein College of Medicine

3. Kathy Freeman
   Statistician

All adverse events will go to the IRB as well as the committee. The committee will meet once a year to review all adverse events and to determine if any further protocol changes are necessary to ensure subject safety and to confirm that the risk vs. benefit has not changed. The committee will then submit a letter to the IRB after the meeting.

Participant Recruitment and Informed Consent

Patients requiring third molar extractions who meet the inclusion criteria for the study will be recruited. These patients are obtained via walk-in emergencies and referrals from within the Montefiore Medical

Center general dental and orthodontic departments. Patients will have the option of having the procedure done without IVS.

Informed consent will be obtained by one of the investigators prior to IV placement. The full protocol including risks, benefits and alternatives will be provided to subjects in writing, and the subject will have the opportunity to ask questions. Consent will be available in English and Spanish with necessary interpreters. A third party will witness all consents. Only subjects with capacity to sign informed consent will be included. Oral consent will also be obtained from the surgeons.

The patient will receive a copy of the informed consent form.
HIPAA authorization will also be provided and signed by every study participant.

Statistical Analysis

Observed respiratory adverse events in children given sedation were 6.1% on ketamine v. 19.3% on midazolam/fentanyl.[18] The relative magnitude of these rates was consistent with the 5% v. 15% rates for respiratory adverse events presented in a power analysis for the comparison of IV and IM ketamine.[19] Thus for α=.05, two-tailed test with 80% power, 114 subjects are required per group. If 5% of subjects change their mind after randomization with regard to participating, then 120 are required per group.

Descriptive statistics for continuous variables will be presented as means and standard deviations, or if non-normal, by medians and ranges. Differences in means between groups at each time point will be presented as their difference with a 95% confidence interval for the difference, and displayed using a line plot with standard error bars. Categorical variables will be summarized using relative frequency distributions, with differences between groups and associated 95% confidence intervals. Histograms will be presented for non-normal continuous variables and relative frequencies.

Comparison of the groups with regard to the proportion of patients with at least one adverse respiratory event requiring intervention during sedation will be assessed using a Fisher's Exact test. The distribution of the number rating score for patient satisfaction will be assessed (VAS scales have been supported for their ratio scale properties), and if assumptions are met, an optimal mixed effects model (with repeated measures over time) will be derived after evaluating various covariance matrix structures. Because patient, physician, and grade of operating conditions will be evaluated at the end of the trial only, and because these scales are ordinal, Wilcoxon Rank Sum tests will be used. To evaluate the differences in hemodynamic stability and respiratory rate, mixed effects models will be derived for heart rate, systolic and diastolic blood pressures, and respiratory rate considering repeated assessments over time. For the number of O_2 saturation events $\leq$92%, and for each of the numbers of respiratory events requiring intervention, Poisson regression with a log link function will be used; in addition multi (recurrent)-event survival models (i.e. Anderson-Gill; Wei-Lin-Weissfield; Prentice, Williams, Peterson) will be applied and the optimal model chosen to determine whether there is a significant difference in the relative number of events that occurred as well as the difference in the distribution (spacing) of these events over the observed time period. To assess whether dexmedetomidine significantly increases postoperative recovery time when compared with propofol, a transformation of scale will be derived to better

approximate normality, and a difference between the groups with regard to recovery times will be assessed using a t-test for independent samples. This procedure will also be performed for time to ambulation and time to "virtual discharge." Because the Aldrete scale is ordinal and assessed only once, the difference between groups will be tested using a Wilcoxon Rank Sum test. All tests of hypotheses will follow an intention-to-treat protocol, will be two-tailed with α=.05, and performed using SAS Version 9.3, Cary, NC. Results will follow CONSORT guidelines. The trial will be registered with clinicaltrials.gov.

Cost

The subjects' insurance will be billed for the treatment. There will be no additional cost to the patient. There will be no reimbursement for travel or compensation for participation.

Collaborations

- Results of the study will be shared Montefiore IRB. This information will contain no identifiers of the involved subjects

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